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Mesenchymal Stem Cell Therapy for Treatment of Diabetic Neuropathy: A Novel Approach

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Abstract: One of the most common complications of diabetes is diabetic neuropathy, which usually leads to foot ulcers and even limb amputations. In diabetic neuropathy, peripheral nerve vascularity is diminished, and angiogenic and neurotrophic factors are lacking. There is still no cure for diabetic neuropathy despite continual improvements in anti-diabetic drugs. Protein or gene therapy is used to treat diabetic neuropathy, although the therapeutic effects are quite limited. Mesenchymal stem cells (MSCs) have been proposed as a unique, emerging regenerative treatment for diabetic neuropathy. Diabetic neuropathy symptoms can be reversed by MSC therapy. MSCs have a crucial role in blood sugar regulation and tissue repair. They can also secrete neurotrophic, angiogenic, cytokine, and immunomodulatory substances in a paracrine way to cure diabetic neuropathy. The clinical use of MSC therapy currently confronts several challenges, including safety, determining the appropriate dosage to use, the best way to deliver cells, issues with MSC heterogeneity, etc. In this review, focus will be placed on the pathophysiological mechanisms driving diabetic neuropathy, MSC features, the effects of MSC therapy on diabetic neuropathy, and issues with MSC therapy.

Keywords: Diabetes, Diabetic neuropathy, Stem cell, Mesenchymal stem cell, microvascular and macrovascular complications

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Introduction

The rising prevalence of diabetes is a known global problem, and developing countries like India, China, and Africa are likely to be most affected in terms of healthcare expenses as well as human suffering, morbidity, and mortality (Lee *et al.*, 2012). Worldwide, it is estimated that 415 million adults have diabetes and another 318 million have impaired glucose tolerance, putting

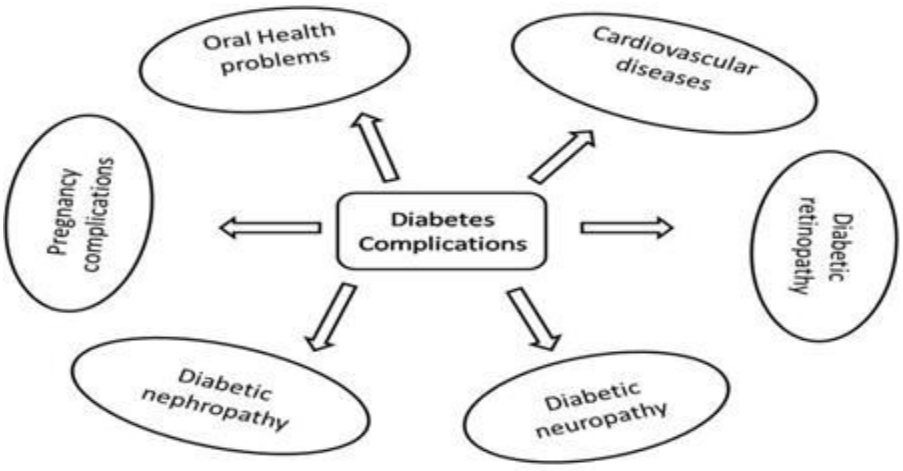

Fig. 1: Diabetes complications.

them at a high risk of developing the disease in the future (Zang *et al.*, 2017). It is well known for being susceptible to multiple complications that seriously impair patients' lives and health, some of which even result in fatalities (Feldman *et al.*, 2019). Increased morbidity, disability, and death due to diabetic complications are concerning for the economies of all nations, but particularly emerging ones (Bisht, 2019). Annually, millions of dollars are spent globally on diabetes-related health expenses (Bisht, 2021). Reactive oxygen species (ROS) production and aberrant alterations in gas transmitters are just two of the numerous mechanisms that have been identified so far for the problems of diabetes, which eventually cause damage to cells, tissues, and organs (Feldman *et al.*, 2019).

Significant increases in the prevalence of diabetes have been seen in almost every part of the world in recent decades. Due to a higher prevalence of diabetes-specific complications, the rise in the number of individuals with diabetes or those who have had it for a longer period is anticipated to change the disease profile in many communities around the world (Harding *et al.*, 2019). Over time, diabetes can cause major complications and have an impact on a variety of organ systems across the body. Diabetes complications can be categorized as microvascular or macrovascular. Microvascular problems can harm the nerve system (neuropathy), the kidneys (nephropathy), or the eyes (retinopathy). Peripheral vascular disease, heart disease, and stroke are examples of macrovascular problems (Deshpande *et al.*, 2008) (Fig. 1).

The most typical microvascular complication in people with diabetes is Diabetes Neuropathy (DN) (Nagaishi *et al.*, 2016) after 20 years of disease development, more than 50% of DM patients have this condition, which has a substantial negative influence on their quality of life given the DM-specific chronic pain in their lower limbs (Bondar *et al.*, 2021). DN is a gradual, systemic condition, and it takes years for the symptoms to appear (Zhou *et al.*, 2016). It is the most frequent type of neuropathy, the most prevalent diabetes complication, and the main cause of impairment, foot ulceration, and ultimately amputation (Maher, 2020). Diabetic neuropathy is a loss of sensory function that begins distantly in the lower limbs and is additionally characterized by discomfort and significant morbidity. At least 50% of people with diabetes eventually get diabetic neuropathy (Feldman *et al.*, 2019). The development and progression of DN are strongly influenced by

hyperglycemia (Bondar *et al.*, 2021). Progressive neuronal loss, demyelination, damaged nerve regeneration, and eventually nerve fiber dysfunction are characteristic features of DN, which affects both the somatic and autonomic branches of the nervous system. The vasa nervorum of the peripheral nerves suffers damage from hyperglycemia, including the neurons, Schwann cells, and endothelial cells. Sensory, motor, and autonomic nerve damage also occurs due to oxidative stress, reactive oxygen species formation, and the creation of advanced glycation end products caused by hyperglycemia (Zhou *et al.*, 2016).

DN is a serious long-term microvascular consequence of both type 1 and type 2 diabetes. The primary symptom of established DN is microalbuminuria, which is then followed by glomerular hypertrophy, a modest expansion of the mesangial matrix, and thickening of the glomerular capillary walls. The main structural feature of DN is glomerulosclerosis, which is brought on by extracellular matrix accumulation, fluid retention, high blood pressure, progressive albuminuria, glomerular basement membrane (GBM) thickening, mesangial cell expansion, and destabilization of podocyte foot processes (Han *et al.*, 2013).

Pathogenesis of DN:

Though the exact origin of DN is yet unknown, metabolic and ischemic factors have been believed to be involved. Rheological alterations caused by hyperglycemia increase endothelial vascular resistance and decrease blood flow to the nerves. Through a mechanism of competitive absorption, hyperglycemia also reduces the amount of myoinositol in the nerves. Furthermore, sorbitol and fructose accumulate in the nerve as a result of the polyol pathway in the nerve being activated by the enzyme aldose reductase, which also causes structural nerve proteins to undergo non-enzymatic glycosylation. Oxidative stress is a significant effect of hyperglycemia. Vascular injury in DN has been associated with protein kinase C activation. As a result of these modifications, the metabolism of neuronal, axonal, and Schwann cells is aberrant, this impairs axonal transport. Increased vascular resistance and decreased blood flow within the nerve result in endoneural hypoxia. Hypoxia causes further capillary damage, which worsens the disruption of axonal transport, lower Na-K ATPase activity, axonal atrophy, and impaired nerve conduction (Bansal *et al.*, 2006). Various pathogenic factors of diabetic neuropathy are shown in Figure 2.

Although anti-diabetic drugs continue to progress, diabetic neuropathy currently has no proven cure. Although the disease's progression may be slowed with the best foot care and glucose management techniques, nerve damage cannot be reversed over time and frequently has life-altering side effects. Healing wounds is difficult, and using medications merely to alleviate the symptoms has little success (Kim *et al.*, 2012). Protein or gene therapies are used to treat diabetic neuropathy, although they have extremely limited therapeutic effects (De Figueiredo and Dos Reis, 2021).

According to the stage of development, stem cells can be separated into two categories: embryonic and adult. Adult stem cells are the undifferentiated cells in differentiated tissues that are seen in a variety of bodily tissues and organs (Huang and Yang, 2021). Recent research on the potential for tissue regeneration in stem cell therapies for the treatment of DN is encouraging. Given their accessibility, immunomodulatory, and pro-regenerative properties, mesenchymal stem cells from different organs and tissues have shown promising therapeutic results. However, problems like rejection of cell transplants, poor engraftment and restricted differentiation of stem cells brought on by the diabetic microenvironment, differentiation into unwanted cell lineages, tumor development, and genetic aberrations of stem cells, transplantation safety, and efficacy, need to be addressed (Liu *et al.*, 2020; De Figueiredo and Dos Reis, 2021). Recently, mesenchymal stem cell (MSC) therapy has drawn increased attention. Cells known as MSCs are being studied to cure human diseases. They have been discovered in

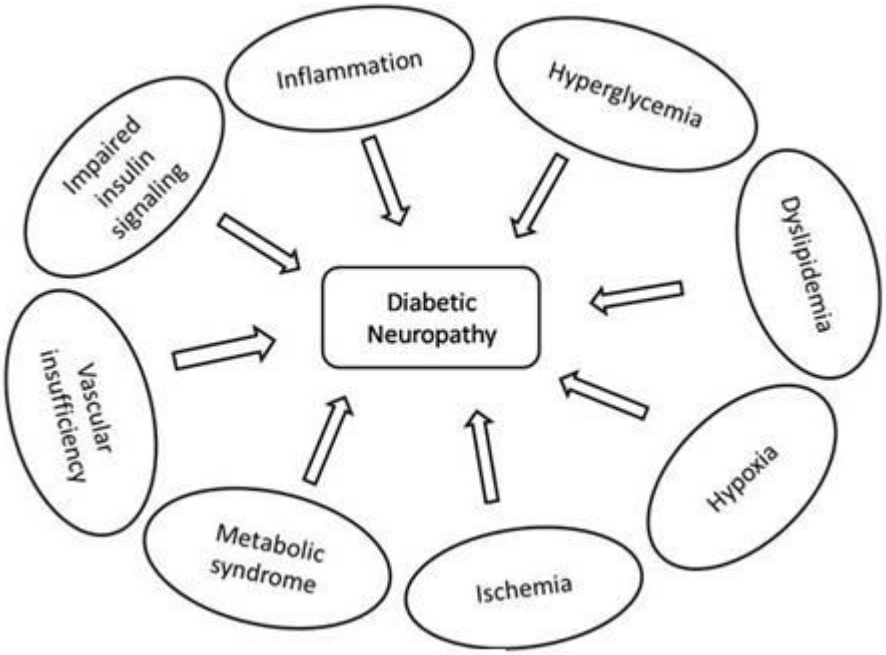

Fig. 2: Pathogenic factors of diabetic neuropathy.

numerous tissues, such as adipose tissue, peripheral blood, tooth pulp, bone marrow, and neonatal tissues, especially in the placenta and umbilical cord (Han *et al.*, 2013; Huang and Yang, 2021).

Mesenchymal Stem Cells:

Mesenchymal stem cells (MSCs) are multipotent, self-renewing cells with the ability to secrete a variety of biological substances that can help heal and rebuild damaged tissues. The therapeutic value of MSCs in a variety of medical disorders has been supported by preclinical and clinical research. The terms "mesenchymal stem cells" and "mesenchymal stromal cells" are currently used most frequently to refer to MSCs. The phrase "medicinal signaling cells" has lately been proposed by some academics (Han *et al.*, 2013). MSCs are currently the most often employed cell-based therapy in clinical trials due to their capacity for regeneration, simplicity in isolation, and minimal immunogenicity. MSCs have shown promise in both experimental and clinical studies used to treat diabetes (Moreira *et al.*, 2017).

The benefits of using MSCs as prospective substitutes for treating disease are summed up in the following six areas (Yan *et al.*, 2021):

(i) It is simple to obtain MSCs from a range of autologous or allogeneic adult tissues, such as bone marrow, adipose tissue, umbilical cord blood, skeletal muscle, synovium, spleen, thymus, lung, and amniotic fluid; they can also be obtained from commercial suppliers.

(ii) MSCs are easily and quickly isolated, and *in vitro* techniques allow for fast cell multiplication.

(iii) MSCs can develop into a range of mesodermal lineage cells as well as endodermal or ectodermal cells.

(iv) MSCs can migrate specifically to the locations of wounded tissues.

(v) MSCs have low immunogenicity, and allogeneic or autologous engraftment has not resulted in any negative reactions.

(vi) There are no ethical issues with using MSCs.

The use of MSCs in the treatment of DPN is remarkable. MSCs can be identified by several markers, including CD54/CD102, CD166, CD73, CD90, CD44, and CD105 (Liu *et al.*, 2020; Akter *et al.*, 2023).

Immunomodulatory ability, capability for self-renewal, and differentiation into tissues of mesodermal origin are the three basic functional

traits of MSCs. Interleukin (IL)-10 production is raised and interferon-gamma (IFN-) and IL-12 production is lowered when MSCs modify the secretion profile of dendritic cells (DCs) through the synthesis of soluble substances. By binding the inhibitory protein programmed death 1 (PD-1) to its ligands PD-L1 and PD-L2, MSCs can produce soluble factors that limit T-cell proliferation (such as TGF- or IL-10) and interact with DCs to reduce T-cell proliferation. MSCs can boost the proportion of CD4+CD25+FoxP3+ T-regulatory cells, which are responsible for reducing the immunological response (Volarevic *et al.*, 2011).

MSCs were identified as promising new therapeutic agents for the treatment of problems of diabetes mellitus (DM) due to their multipotent differentiation properties, capacity for self-renewal, and ability to regulate immunological responses (Volarevic *et al.*, 2011). MSCs secret neurotrophic and angiogenic factors. Neurotrophic factors, also known as neurotrophins (NTs) are the growth factors that help in the survival and regeneration of neurons. Neurotrophic factors include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factors (GDNF) etc. (Xiao and Le, 2016). Additionally, they aid in regeneration, regulate neuronal plasticity, and aid in the recovery of damaged neurons. They also keep the cell's functionality intact (Huang and Reichardt, 2001; Zhou *et al.*, 2016). Lack of neurotrophic factors contributes to the development of diabetic neuropathy (Zhou *et al.*, 2016).

Vascular endothelial growth factor (VEGFs) is one the most important angiogenic factor that plays an important role in the development of DN (Zhou *et al.*, 2016). In endothelial cells, VEGFs stimulate the development of blood vessels by activating a family of cognate receptor kinases (Holmes and Zachary, 2005; Kim *et al.*, 2012). Likewise, VEGF stimulates axonal development and survival of both the neurons and Schwann cells of the superior cervical ganglia and dorsal root ganglia. It also improves Schwann cell migration and proliferation (Kim *et al.*, 2012). Numerous prominent growth factors, recently named angiotensin, have the dual effects of being both neurotrophic and angiogenic. Examples include brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), nerve growth factor (NGF), and fibroblast growth factor-2 (FGF2) (Han *et al.*, 2013; Zhou *et al.*, 2016).

MSCs Therapeutic Mechanism:

According to the current theory, exogenously administered MSC treatment works by homing in on the areas of injury and differentiating into adult cell types. For cell survival, transplanted MSCs emit soluble factors, such as cytokines, chemokines, interleukins, and secondary messenger molecules, and insoluble or physical factors, such as biomechanical stresses, ions, and so on. The factors that are released influence both cell death and pro-survival pathways. These elements additionally improve the tissue repair processes that reverse disease (Chandramoorthy *et al.*, 2017).

Glycemic Control by MSC:

MSC implantation may directly result in the production of cells that can produce insulin; however, this is less likely than the development of immunomodulators that stop T cells from causing the degeneration of pancreatic beta-cells (Zhou *et al.*, 2016). Diabetes symptoms in type 1 diabetic rats are attenuated by MSC differentiation into cells that generate and release insulin in a glucose-dependent manner. Numerous genes involved in the growth or operation of pancreatic cells are expressed by these insulin-producing cells (Zhou *et al.*, 2016; Wang *et al.*, 2021).

Additionally, MSCs help to increase insulin sensitivity which is a critical stage in the pathological development of DM, particularly in type 2 diabetes. It has been suggested that the early phase of MSC infusion boosted -cell function and also improved insulin resistance, whereas the late phase of infusion just improved insulin resistance (Si *et al.*, 2012; Wang *et al.*, 2021). Through cell-to-cell interaction mediated by the

adhesion molecule N-cadherin, MSC is also found to increase the lifespan and efficiency of islets of Langerhans (Montanari E, 2017). Multiple intravenous MSC infusions normalized hyperglycemia, which remained stable after 9 weeks following infusion, with reduced serum levels of insulin and C-peptide, and reverted damaged pancreatic islets to almost normal function (Zhou *et al.*, 2016).

Neurotrophic and angiogenic factors releasing effect of MSCs:

To stimulate axonal development, immunomodulation, angiogenesis, remyelination, and protection against apoptotic cell death, MSCs produce anti-inflammatory, antiapoptotic compounds as well as trophic substances into the damaged milieu of the central nervous system. By enhancing the microcirculation that supports peripheral nerves, MSCs are known to support angiogenesis mostly through a paracrine effect (Zhou *et al.*, 2016). In addition to directly differentiating into neurons and endothelial cells after transplantation, transplanted MSCs also release higher levels of physiologically active substances such as FGF, VEGF-A, and NGF, which are essential for the health of vascular and neural tissue (Han *et al.*, 2013; Zhou *et al.*, 2016).

Release of Trophic factor (*Exosomes*) *by MSCs*:

One extracellular vesicle (EV) called exosome is a new method of MSC-based therapeutics for tissue regeneration. These trophic factors are either naturally present in secreted membrane vesicles with a diameter of 30–40 to 100–120 nm or are released from MSCs in a free state or contained within exosomes. In addition to transferring receptors, proteins, and genetic information (mRNA and microRNAs), these extracellular vesicles are thought to be crucial mediators of cell-to-cell communication (Han *et al.*, 2013). Exosomes produced by mesenchymal stem cells (MSC-Exos) have been shown to be just as effective as MSCs in the treatment of diabetes and its complications. In comparison to the parental cells, MSC-Exos have shown in some trials to have a stronger therapeutic and regenerative effect in treating T1DM (Yang *et al.*, 2022).

Reduction in Pro-Inflammatory Activity by MSC Therapy to Treat Diabetic Peripheral Neuropathy:

MSCs control immune cell filtration and migration directly, which lowers inflammatory activity (Zhou *et al.*, 2016). Important cells involved in inflammatory disorders include macrophages (Jin *et al.*, 2022). The activation of the chemokines CCL2, CCL3, CCL4, and CCL5, as well as the pro-inflammatory cytokines IL1 and IL6, causes inflammation. These cytokines and chemokines influence the development of inflammation, tissue healing, and immunological responses by attracting immune cells and controlling autocrine and paracrine actions (Jin *et al.*, 2022). MSCs can control innate and adaptive immunity and have considerable immunomodulatory capacity (Jin *et al.*, 2022). In research, MSCs were injected intravenously to treat diabetic rats' kidney fibrosis and diminish renal CD68+ macrophage infiltration and inflammatory cytokine expression. MSCs affect immune cell filtration, which reduces inflammatory responses. Additionally, EMT and fibrosis processes are delayed together with the anti-inflammation of MSCs in DN (Zhou *et al.*, 2016).

The Challenge of MSC Therapy:

The use of MSCs to treat DN has recently undergone substantial investigation in preclinical animal models, and the majority of publications indicate beneficial effects on DN (Zhou *et al.*, 2016). Cell treatments are still currently only used in animal models, and most data indicate that they are effective for treating DN. These researches have, however, shown certain specific challenges (Yang *et al.*, 2022).

Even though MSC therapies protect against neuro-degeneration and encourage neuro-regeneration, there seem to be numerous challenges to be overcome before they may be used in clinical settings. These challenges (Fig. 3) are as follow:

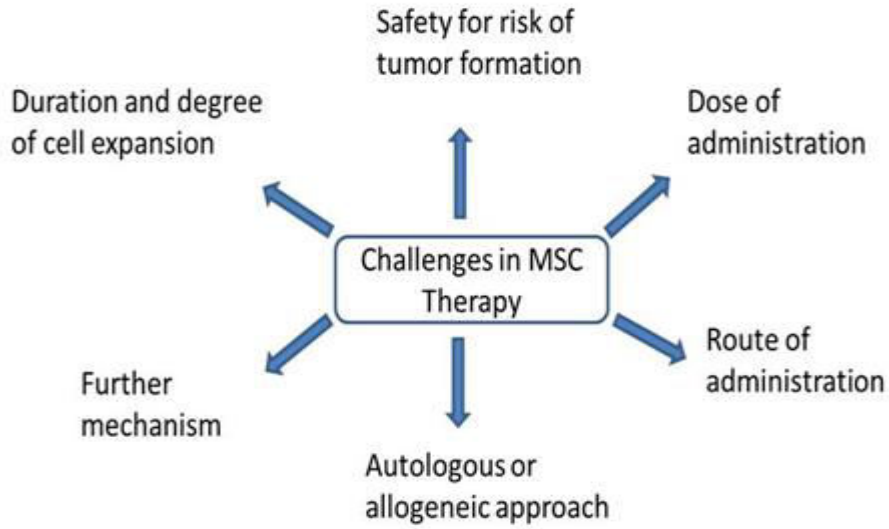

Fig. 3: Challenges with MSC therapy.

(1) The ideal dose of administration

(2) Safety

(3) The route of transplantation

(4) Autologous or allogeneic approach

(5) Additional mechanisms and

(6) Clinical end points for the efficacy of MSC therapy

Even though MSC transplantation has been the subject of several studies in both patient and animal models, it is still unknown what exact mechanisms underlie their positive effects. For the pathological long-term effects of diabetes on the host system to be properly shown in preclinical animal models, adequate preclinical animal models are needed.

Conclusion

Without appropriate therapeutic treatment, DN frequently results in foot ulcers and eventually limb amputation. Due of their versatility for DN, MSCs have been emphasized as a new developing regenerative therapy. MSCs repair tissue, treat hypoglycemia, and reverse DN symptoms. In order to treat DN, MSCs also produce neurotropic, angiogenic, cytokine, and immunomodulatory chemicals via paracrine mechanisms. Safety, optimum administration dose, optimum cell delivery method, problems with MSC heterogeneity, clinically significant engraftment, autologous or allogeneic approach, difficulties with cell production, and additional mechanisms are obstacles in the clinical translation of MSC therapy. The findings of the MSC applications are varied and positive in several therapeutic approach areas, indicating the necessity for additional research.

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