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Cell Therapy for Diabetic Neuropathy

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1. Introduction

A debilitating consequence of diabetes mellitus (DM) is neuropathy which globally affects between 20 -30% of diabetic patients and up to 50% [1, 2]. The lifetime incidence of diabetic neuropathy (DN) is estimated to be up to 45% for type 2 diabetic patients and 59% for type 1 diabetic patients in USA. The risk of DN rises with age, duration of DM, and vascular disease. Characterized by damages in the arms and legs, peripheral neuropathy is the most common complication of DM.

The pathophysiology of DN is promoted by several risk factors: microvascular disease, neural hypoxia, and hyperglycemia-induced effects. At the molecular level, the primary cause of diabetic complications is known to be hyperglycemia, which disrupts cellular metabolism by the formation of reactive oxygen species (ROS). In the aspect of nerve functions, ROS formation increases neuron's susceptibility to damage. In addition, hyperglycemia impedes production of angiogenic and neurotrophic growth factors, which are necessary for normal function of neurons and glial cells and maintenance of vascular structure.

The most common presentation of nerve damage due to the effects of hyperglycemia is neuropathic pain. Peripheral neuropathy may cause foot deformities such as hammertoes and unnoticed sores and infections in the numb areas of the foot. Improperly treated infection frequently extends to the bone and requires an amputation of the foot.

There have not been any definitive disease-modifying treatments to reverse DN. The current treatment focuses on tight glycemic control which can reduce potential risk factors for further nerve damage and DN-associated pain management. In many studies, deficiency of neurotrophic factors and lack of vascular support have been regarded as key factors in the development DN. Therefore, cell therapy has recently emerged as an attractive therapeutic strategy to meet the needs of both neurotrophic and vascular deficiencies of DN.

2. Symptoms, signs and diagnostic tests

DN most often starts with hypesthesia (diminished sensation) of the lower extremities, which extends to a stocking-glove distribution. The most feared complications are foot pain, ulcerations and amputation, which increase morbidity and mortality thereby reduce the patient's quality of life [3]. Proper diagnosis of the etiology of DN depends on the pattern of sensory loss, reflex test, electrodiagnostic studies, and imaging. In electrodiagnostic studies, nerve conduction velocity and magnitude are measured by electrically stimulating nerves.

Peripheral nerve imaging such as ultrasound and magnetic resonance imaging (MRI) are used for evaluating the extent of peripheral nerve pathology. They give insight to which type of nerve fiber is affected.

3. Pathophysiology

DN, nerve damage caused mainly by glycemic dysregulation, is the most common complication of DM. Prolonged hyperglycemic episodes result in a complex series of metabolic and vascular damages which contribute to the multi-factorial etiology of DN [4, 5]. The major pathogenetic factors are hyperglycemia-induced metabolic derangements which cause excess oxidative stress and loss of neurovascular support.

In general, immediate pathologic effects of hyperglycemic episodes are metabolic in nature. However, electrophysiologic and morphologic alterations seem to be late occurrences. There are various pathologic changes that occur in DN. Pathologic changes in peripheral nerve are endoneurial microangiopathy, nerve demyelination, loss of nerve fibers, axonal degeneration, axonal dystrophy and Schwann cell abnormalities[6, 7-9].

3.1 Oxidative stress to cellular damage

Hyperglycemia-induced oxidative stress has been proposed as a single unifying mechanism of neurodegeration in DM by Brownlee et al. [10]. Hyperglycemia cause metabolic abnormalities which result in mitochondrial superoxide overproduction in peripheral nerves [11] and supporting vasculatures [10, 12].

Hyperglycemic environment induces activation of 5 pathways involved in the pathogenesis of diabetic microvascular complications [13]. These include: the polyol pathway[14]; nonenzymatic glycation of proteins which increases advanced glycation end-products (AGEs) [15, 16]; hexosamine pathway flux [17]; protein kinase C (PKC) pathway [18] which triggers stress responses; and the poly ADP-ribose polymerase (PARP) pathway [19, 20]. Increased activity of the 5 pathways deplete antioxidants which are necessary for antioxidant defense system against free radicals. The hyperglycemia-mediated superoxide overproduction perturbs the five pathways, and thereby causes metabolic and vascular imbalance and initiates the progression of neurovascular dysfunction [21-23].

In polyol pathway of glucose metabolism, aldose reductase catalyzes the NADPH-dependent conversion of glucose to sorbitol [14]. Aldose reductase also competes with glutathione reductase in NADPH-dependent production of Glutathione (GSH), a major antioxidant in cells. A high level of glucose overactivates the polyol pathway thereby depleting NADPH necessary for GSH antioxidant production. Consequently, insufficient GSH level contributes to accumulation of ROS.

In hexosamine pathway of glucose metabolism, its overactivation diminishes antioxidant production. This also increases posttranslational modification of specific amino acid residues on cytoplasmic and nuclear proteins, and thereby changes their functions [17].

In DM, high levels of AGEs is found in extracellular matrix. Thus, plasma proteins enhanced with advanced glycation bind to Receptor for AGEs (RAGE) on cells such as macrophages and vascular endothelial cells. This activates pleiotropic transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) which results in multiple pathological changes in gene expression. The interaction between RAGE and AGEs is shown to cause pro-inflammatory gene activation [24]. Myelin is considered a major target for such

non-enzymatic modification by glucose. Reactive and degenerative Schwann cell changes lead to demyelination which is the dominant lesion of peripheral neuropathy. The decrease in the density of myelins affects both large and small nerve fibers. Hyperglycemic condition causes consistent demyelination and axonal degeneration and presents aberrations in nerve regeneration.

Activation of PKC pathway leads to inhibition of Na+/K+ ATPase which in turn leads to decreased endothelial nitric oxide synthase (eNOS). Consequently, eNOS reduction results in blood-flow abnormalities and vascular occlusion caused by increased transforming growth factor beta (TGF-B) and plasminogen activator inhibitor-1 (PAI-1). PKC pathway activation also increase NF-kB expression which results in proinflammatory response and dysfunction in sending electrical signals in neurons. As a result, the nerve conduction level diminishes, and thereby obstructs nerve regeneration.

In healthy cells, ROS production is tightly controlled. The antioxidant defense system of a cell responds to the environmental changes [25]. However, in diabetic environment, cells end up with accumulated ROS which alter proteins and their functions. Superoxide accumulation can have direct, toxic damages to Schwann cells. This leads to decreased neuron insulation causing ineffective signaling, weakened immunologic perineurial blood-nerve-barrier, and reduced nerve regeneration. Studies showed that oxidative stress impairs vasodilation of epineural blood vessels, resulting in ischemia to the neural tissue [26-28].

3.2 Loss of neurotrophic and vascular support

Oxidative stress majorly contributes to the development of DM complications, both microvascular and macrovascular [13]. The confluence of metabolic and vascular disturbances in nerve causes impairment of neural function. There are clear evidences that insufficient vascular support and neurotrophic factors play a major pathophysiologic role in DN. Studies show decreases in nerve and angiogenic growth factors in nerves from animals with experimental DN [29, 30]. The emphasis placed on the fact that animals with DN show a deficiency in growth factors with both angiogenic and neurotrophic function. This seems to play significant role in pathogenesis of DN.

3.2.1 Growth factor deficiency

There are specific growth factors that guide blood vessels and nerves to their tissue targets, and their deficiency plays a significant role in the pathogenesis of DN. Many representative growth factors display pleiotropic effects which are both neurotrophic and angiogenic [31]. To underline their duality, the growth factors that have both angiogenic and neurotrophic effects are referred to as, “angioneurin” [32]. For example, vascular endothelial growth factor (VEGF) was originally discovered as growth factors specific for endothelial cells [33]. While VEGF was originally known to play a key role in promoting angiogenesis, studies showed that it directly affects the neural growth, neural survival and protection (neurotrophic), and axonal outgrowth (neurotropic) [31]. Thus, VEGF which was once regarded as a specific angiogenic factor is now implicated in neuroprotection.

Similarly, nerve growth factor (NGF), known to promote neurotrophic and neurotropic effects in neuronal cells [34-36], also have angiogenic effect on endothelial cells. Since nerve growth factors (NGF) promote maintenance, survival and regeneration of nerves, a decrease in NGF synthesis causes functional deficit of nerve fibers [37].

VEGF and NGF are not the only examples of angioneurin. Another representative angioneurin involved in pathogensis of DN is insulin-like growth factor (IGF) [38-40]. IGFs are know to promote growth and differentiation of neurons. In addition, IGFs is also found to exert favorable effects on angiogenesis [41]. Insulin deficiency in diabetic state causes reduction in IGFs level in circulation. This abnormal metabolism of angioneurins adds to pathogenesis of DN. Several studies have shown that diabetic animals showing decreased level of angioneurins highly correlates with reduced neural and vascular function [42, 43].

3.2.2 Vascular deficiency

Initially, the focus has been on the hyperglycemia-induced metabolic changes and their direct neuronal effects. However, studies in animal models showed that they also have vascular targets linked to neuropathy [44].

The vascular alterations observed in human and animal models of DN include: thickening of basement membrane of vasa nervorsa[6, 36, 45-48] strongly related to severity of DN [45, 49, 50], decrease in nerve conduction velocity (NCV) in rats with impaired vasodilation in epineurial arterioles [26-28]., changes in luminal areas of endoneurial capillaries, and changes in endoneurial capillary density. Studies on measures of luminal areas of endoneurial capillaries showed different findings. Rodent and feline models of DN showed increase in luminal areas of endoneurial capillaries[51-54].

Conversely, studies on human showed various results. They showed that luminal areas increased [45, 46, 55], unaltered [36, 48, 56], or decreased [6, 47, 49, 57, 58]. Similar to measures of luminal areas, the measured density of endoneurial capillaries also showed mixed results. Studies on animal models showed that the density was increased [53, 59], unaltered [60], or decreased [42, 43, 61]. As well as in human, the results were mixed. A study showed that the density of endoneurial capillaries was increased in patients of early stage DM than healthy subjects [56], while the density of those with established neuropathy and late stage DM was similar to that of normal people [36, 45, 49].

The complex series of oxidative stress-related metabolic changes result in reduced nerve perfusion and ischemia [23, 62]. Impaired blood supply to nerve and ganglion and endoneurial hypoxia play a significant role in causing DN. Specifically, impairment of blood supply to neural tissues through vasa nervorum, blood vessels of peripheral nerves prompt pathogenic mechanisms of DN [62].

Thrainsdottir et al. [56] reported vascular structural alterations caused by early diabetic condition. Blood vessel number in diabetic nerves increased in response to ischemia in early DM. However, the blood vessel number decreased due to impaired neovascularization under prolonged diabetic condition [6].

One of the major pathogenic factors in the development of DN is reduced nerve blood flow (NBF). Various clinical and experimental studies give evidence that amelioration of NBF improved nerve functions. Studies on diabetic patients reported decrease in endoneurial blood flow and presence of hypoxia compared to healthy subjects. Direct measures of nerve perfusion revealed that DN strongly correlated with decreased sural nerve blood flow [63, 64]. A study by Tesfaye et al. [63] also showed that patients suffering from DN had impoverished endoneurial microenvironment.

Overall, the results of various studies indicate that vascular deficiency is highly represented in established DN. As observed, there was an increased number of capillaries in response to ischemia in early stage DM. Eventually, the number of capillaries decreased. It is plausible that chronic diabetic condition disturbed neovascularization and regeneration [51, 65, 66].

Therefore, debilitating microvascular dysfunction and pathogenic mechanisms altering the the surrounding vascularity damage the peripheral nerve.

3.3 Multifactorial etiology of DN

DN is caused by damages in vessels, neurons, and Schwann cells. Hyperglycemia induces metabolic abnormalities cause overproduction of reactive oxygen species (ROS), activation of inappropriate inflammation pathways, and decreased level of antioxidants such as glutathione. These abnormalities render endothelial and neural cells more susceptible to angioneurin deficiency which finally causes deterioration of neurovascular support in nerves. Ischemia (a restriction in blood supply) and damaged perfusion further stimulates hyperactivity of pathogenic cycles in endothelial cells, neurons, and Schwann cells – resulting in nerve degeneration.

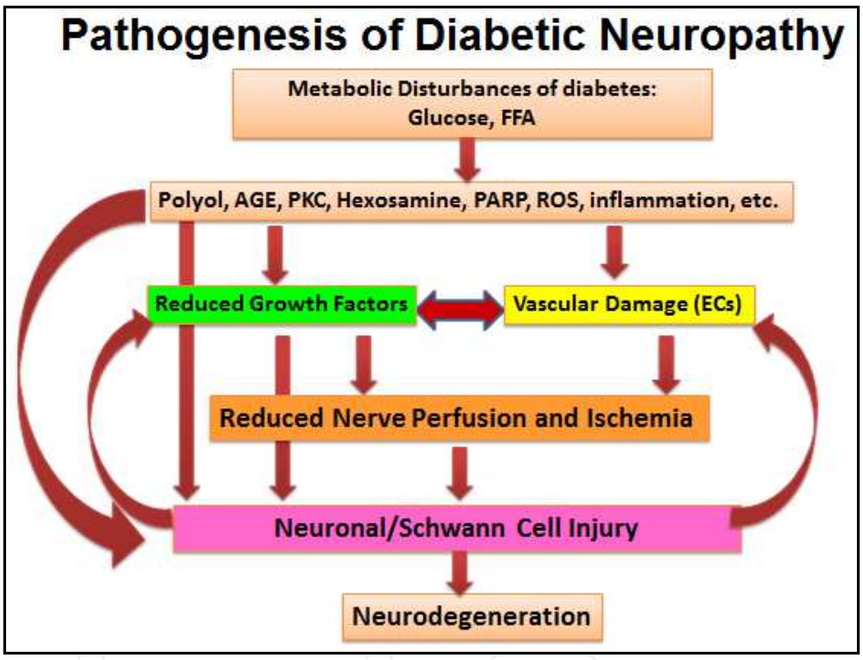

Fig. 1. The proposed pathways that lead to the pathogenesis of DN and interactions at the level of each proposed mechanism. Polyol = Polyol pathway; ECs = endothelial cells.

4. Treatment options and cell therapy

Current treatment strategies focus on preventing neuropathy, slowing its progression, and reducing symptoms and pain. Symptomatic treatment options which are only partially effective include lifestyle interventions, physical therapies, drug-therapies and complementary therapies. Several potential therapies exist for the treatment of DN based on neurovascular pathogenesis. They include: gene, protein, and cell therapies.

Emerging evidence is that angiogenic factors such as VEGF-A, VEGF-C, SHh, and statin can restore microcirculation of the affected nerves and induced functional improvement in DN [61, 62, 67]. On the other hand, lack of neurotrophic factors has emerged as an important pathogenic mechanism of DN [29, 30]. Administration of neurotrophic factors such as NGF

[68], IGF1 and IGF2 [38, 39], ciliary neurotrophic factor (CNTF) [69], or glial cell line-derived neurotrophic factor (GDNF) [70] was shown to ameliorate DN in animal models.
These findings suggest that a therapy targeting both angiogenic and neurotrophic processes may be more advantageous for the treatment of DN. As stem or progenitor cells have such pleiotrophic effects, cell therapy can be more effective than single gene or protein therapy. Cell therapy can provide multiple angiogenic and neurotrophic factors as well as specific type of cells required for vascular or neuronal regeneration (Fig 1). Currently, various bone marrow (BM) cells were shown to have favorable effects for treating DN.

4.1 Therapeutic potential of bone marrow mononuclear cells

Bone marrow (BM) is a source mononuclear cells (MNCs). Bone marrow-derived mononuclear cells (BM-MNCs) are heterogeneous group of cells which include at least: endothelial progenitor cells (EPCs) and the mesenchymal stem cells (MSCs). MSCs are speculated to differentiate into the cellular components of vascular structures [71]. An advantage of using circulating or BM-derived cells is that they can be harvested from a patient's own peripheral blood or bone marrow, and re-introduced back to the patient [72, 73].
Studies have shown the beneficial effects of using BM-MNCs. They improved neovascularisation by increasing levels of angiogenic factors such as VEGF, FGF-2, and angiopoietin-1 [102, 103]. In patients with ischemia, BM-MNCs transplantation has also been reported to be beneficial [104]. Because bone marrow derived MSC transplantation has been shown to be an option in treating ischemic diseases [74], there was an in interest of using similar strategy in treating DN.

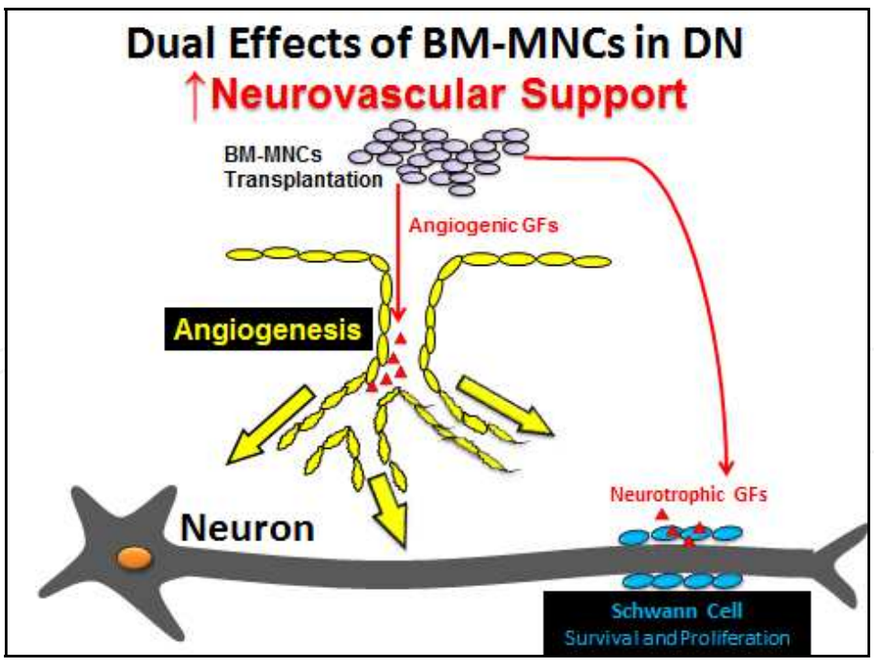

Fig. 2. BM-MNCs induce paracrine effects by releasing angiogenic and neurotrophic growth factors (GFs) thereby increasing neurovascular support in the nerves.

An advantage of using BM-MNCs as source of cell therapy is that they are rather easy to acquire. They can be isolated from bone marrow by centrifugation and do not require ex

vivo culture system. Other advantages of using the BM-derived cells that MSCs and EPCs have proved their therapeutic effects in various clinical and experimental studies of DN.
For example, a study by Hasegawa showed that peripheral blood mononuclear cells (PB-MNCs) or BM-MNCs implantation in rats with DN partially recovered blood flow and improved the NCV of the sciatic nerve [60].
A study by Kim et al. [43] reported that intramuscular transplantation of BM-MNCs preferentially homed in vasa nervorum and increased expression of various angiogenic and neurotrophic factors in the nerves [43]. The study also showed improvement of nerve vascularity and normalization of NCV suggesting that BM-MNC-induced neovascularization is a consequence of angiogenesis (Fig 2). Overall, the emphasis must be placed on the idea that BM-MNCs induce neovascularization and improve manifestations of DN by their ability to promote angiogenesis. Also the safety of autologous BM-derived cells was reported by clinical trials [75].

4.2 Endothelial progenitor cells and vasculogenesis

There are two processes involved in blood vessel formation: vasculogenesis and angiogenesis. Vasculogenesis is the process of formation of blood vessels from *de novo* productions of endothelial cells which may have differentiated from angioblasts or endothelial progenitor cells [76]. Conversely, angiogenesis is the pre-existing vessel growth by vessel formation blood vessels through proliferation and migration of endothelial cells [77]. Thus, endothelial cells are of great interest because of their ability to form blood vessels thereby potential to regenerate vascular dysfunction in DN.
Endothelial progenitor cells (EPCs) are a heterogeneous subset of BM-MNCs. EPCs are capable for differentiation within endothelial cell lineage and are identified according to expression of hematopoietic stem cell and endothelial cell surface markers. EPCs were initially identified by their expression of surface markers VEGF receptor-2 and CD34 [78-80] However, later studies also used CD133 expression to identify EPCs [4, 81] . The precise defintion and characterization of EPCs are still controversial due to the fact that they don't have a unique marker that solely identifies the EPCs. Various types of EPCs have been known as different culture methods give rise to EPCs with distinct characteristics [82]. Derived from mononuclear cells or monocytes, "Early EPCs", have a short proliferation period which is up to a few weeks [83-85]. Conversely, "Late EPCs" have rapid and longer proliferation period and shaped like cobblestones [83, 86]. The early and late EPCs also express different set of cell surface markers. In addition, therapeutic potential of early EPCs has been reported but that of late EPCs is still questioned [83, 86].
The question of whether the differentiation of EPCs plays a vital role in the recovery of damaged tissue function is still controversial.. Some studies showed that differentiation of EPCs into endothelial lineage cells and they were incorporated into blood vessel formation [87, 88]. However, more recent studies have argued against the fact that EPCs did not differentiate into ECs [89, 90]. Although the major therapeutic effects are not through endothelial differentiation but angiogenesis, overall evidence clearly suggests that BM-derived EPCs partake blood vessel formation through vasculogenesis.
Despite such discrepancies, studies on EPC transplantation in DN animal models appear to reach the consensus that EPCs' therapeutic effects and promotion of neovascularization are primarily caused by paracrine or humoral action, not endothelial differentiation [84, 91]. One study showed that cord-blood derived EPCs was effective for treating DN [92]. This

study claimed that mechanistically, the therapeutic effects are due to the increased differentiation of EPCs into endothelial cells in hind limb muscles, which then led to an increase in sciatic nerve blood flow. However, this study did not demonstrate the fate of the EPCs in tissues, nor did it address the mechanisms by which transplanted EPCs increase neovascularization in muscles or nerve. Given that most recent studies have argued against the endothelial differentiation of EPCs as a major mechanism for neovascularization, endothelial differentiation does not appear to underlie such magnitude of therapeutic effects toward DN [84, 91].

A study by Jeong et al. [42] reported direct augmentation of neural neovascularization in sciatic nerves of mice with DN after local intramuscular injection of BM-derived EPCs. The injected EPCs preferentially homed to peripheral nerves but much less to the muscles. This showed that muscular neovascularization is not the mechanism at work. Also, the study showed EPCs have durable engraftment into diabetic nerve. The engraftment lasted up to 12 weeks, which is a unique behavior of EPCs in peripheral nerves because EPCs normally disappear within a couple of weeks in other tissue types. Another novel finding was that engrafted EPCs were localized close to the vasa nervorum which is the blood supply to the peripheral nerves. These findings clearly indicated that BM-derived EPCs exerted therapeutic effects by directly tartgeting the nerves. At the molecular level, the study showed significantly increased levels of angiogenic and neurotrophic factors in the EPC-injected nerves. They include: VEGF-A[62, 93], FGF-2[94], BDNF[95], SHh[61, 96], and stromal cell derived factor (SDF)-1α [97, 98]. These factors are known to have effects on both angiogenesis and neuro-protection [62, 99, 100], suggesting dual angioneurotrophic effects of EPCs. More direct evidence of such dual effects of EPCs were demonstrated by proliferation of endothelial cells and schwann cells and decreased apoptosis of Schwann cells at the histology level. This study showed previously unexpected and distinct properties of BM-derived EPCs such as peripheral neurotropism, sustained engraftment, vascular localization of EPCs, dual angioneurotrophic effects and reversal of various functional and pathologic features of DN [42, 43, 60, 92].

4.3 Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent cells which are found in nearly all postnatal organs and tissues [101]. The adherent nature of MSCs makes them easy to expand in culture and an attractive candidate to use in cell therapy. Also, MSCs are particularly attractive therapeutic agents because of their ability to self-renew, differentiate into multilineage cell types [102, 103], and locally secrete angiogenic cytokines, including basic fibroblast growth factor (bFGF) and VEGF [74, 104-106]. These factors were reported to prompt neovascularization [107] and have support for neural regeneration [99, 108]

MSC transplantation was reported to be a therapeutic agent in the treatment of cardiovascular disease. Similarly, it was plausible that MSCs may also be an effective therapeutic agent for the DN treatment [74, 109] through the paracrine effects of bFGF and VEGF [110] and their potential to differentiate into neural cells such as astrocytes [111], oligodendrocytes [112], and Schwann cells [113, 114].

A study by Shibata et al. [109] suggested that the MSC transplantation on thigh muscles of STZ-induced rats with DN achieved therapeutic effects. Diabetic rats showed hypoalgesia, decreased nerve conduction velocity (NCV), decreased sciatic nerve blood flow (SNBF), decreased capillary number–to–muscle fiber ratio in muscles. These variables were

improved by intramuscular MSC injection. MSC injection in diabetic rats seems to produce bFGF and VEGF which eventually showed increased muscular and neural blood flow leading to functional improvement [109]. Although MSCs seem to have some ameliorating , paracrinal effects on diabetic nerve fibers [109] they did not seem to differentiate into neural cells.

Despite the beneficial effects of MSC transplant in experimental DN shown previously, there appears to be major limitation in using MSCs for DN therapy. Study by Jeong et al. [115] showed that BM-derived MSCs may undergo chromosomal abnormalities and formed malignant tumors after injection into mice with DN. This study alerts careful monitoring of chromosomal status for transplantation of MSCs from in vitro expansion.

5. Conclusion

Intensive symptomatic treatment and tight glycemic control benefits and amerliorates nerve dysfunction and pain in some patients with DN. However, favorable outcomes of cell therapy using BM-MNCs, EPCs and MSCs emphasize the importance of targeting multiple pathophysiology for effective therapy and the need for future clinical trial. Particularly, EPCs' synergistic action of neurotrophic, angiogenic and vasculogenic properties show great potential as a therapeutic agent.

Cell therapy may not be a standard treatment option for all stages of DN because different stages of DN are marked by different structural or functional changes. At present, cell therapy may be applied to those patients who suffer from intractable symptoms, acute exacerbation, or combined diseases such as diabetic foot ulcers or critical limb ischemia. However, there are a few remaining concerns in cell therapy strategy. The effectiveness of the patient's own cells needs to be evaluated considering the possibility that BM cells derived from diabetic subjects may be impaired in therapeutic potential. Experiments using the autologous cells derived from diabetic subjects are necessary to address these concerns. Also, the long-term effects of cell therapy need to be tested.

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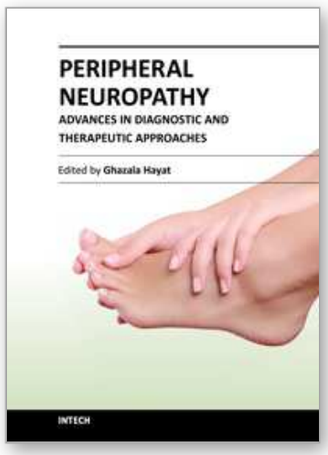

Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches

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Over the last two decades we have seen extensive progress within the practice of neurology. We have refined our understanding of the etiology and pathogenesis for both peripheral and central nervous system diseases, and developed new therapeutic approaches towards these diseases. Peripheral neuropathy is a common disorder seen by many specialists and can pose a diagnostic dilemma. Many etiologies, including drugs that are used to treat other diseases, can cause peripheral neuropathy. However, the most common cause is Diabetes Mellitus, a disease all physicians encounter. Disability due to peripheral neuropathy can be severe, as the patients suffer from symptoms daily. This book addresses the advances in the diagnosis and therapies of peripheral neuropathy over the last decade. The basics of different peripheral neuropathies is briefly discussed, however, the book focuses on topics that address new approaches to peripheral neuropathies.

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