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# Effect of Mesenchymal Stem Cells Transfusion on Diabetic Peripheral Neuropathy

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**Abstract**

The abstract provides a brief summary of a study on the use of mesenchymal stem cells (MSCs) as a potential treatment for diabetic peripheral neuropathy (DPN). The study aimed to evaluate the impact of MSC transfusion on DPN symptoms such as pain, sensory loss, and nerve conduction in 10 patients with DPN. The MSCs were obtained from bone marrow aspirate and were evaluated for surface markers before and after culture. The patients received an intravenous injection of 1 million MSCs/kg in one session. The study found that there was improvement in blood sugar levels and sural nerve amplitude 90 days post-MSCs transfusion and an increase in b-FGF and VEGF levels 7 days post-MSCs transfusion. The conclusion suggests that MSCs transplantation could be a promising treatment option for DPN patients, but further research is needed to optimize the dose, number of sessions, and transfusion method.

**Keywords:** mesenchymal stem cells, diabetic peripheral neuropathy, basic fibroblast growth factor, vascular endothelial growth factor

**Full-length article** **Corresponding Author, e-mail: dina_riad@gmail.com*

## 1. Introduction

Diabetic peripheral neuropathy (DPN) is the most common type of neuropathy in diabetic patients[1,2] and that the risk of developing DPN increases with age, duration of DM, and other vascular diseases[3]. There is currently no disease-modifying cure for DPN [4,5]and that many studies have suggested that mesenchymal stem cells (MSCs) may be a beneficial treatment option due to their ability to self-renew, differentiate into various cell types[6,7], and secrete a variety of cytokines with angiogenic and neuro-supportive properties[8]. The study aims to explore the effect of MSC transfusion on DPN in terms of improving symptoms such as pain, sensory loss, and nerve conduction.

## 2. Subjects and Methods

This study enrolled 10 Egyptian patients with diabetic peripheral neuropathy (DPN) who were chosen from Kasr Al Aini Hospital. The patients were between the ages of 33 and 45, had type I or type II diabetes, and had DPN confirmed by diagnostic testing and nerve conduction, and had not received therapy for DPN. Exclusion factors included decompensated heart, renal, or hepatic problems, accompanying autoimmune diseases, related endocrine problems, pregnancy, and use of contraceptive pills or drugs. The study included a full clinical evaluation, diagnostic tests, and blood tests at the beginning of the study and 90 days after receiving bone marrow-derived mesenchymal stem cells (MSCs) via transfusion. The MSCs were obtained by puncturing and collecting bone marrow, separating and expanding the cells in a laboratory, and then injecting 1 million MSCs/kg into the patients in one session. Follow-up evaluations were done after 3 months and included clinical examination, laboratory tests, and nerve conduction studies. The study also used flow cytometry and ELISA to analyze the surface expression of MSCs and measure b-FGF and VEGF levels in the patients. Data was analyzed using statistical tests such as t-test, ANOVA, and chi-squared test.

### *2.1. Methods*

#### *2.1.1. Sample collection*

The procedure of bone marrow (BM) collection was performed by utilizing sterile syringes coated with preservative-free heparin (Sigma-Aldrich, St. Louis, USA) to prevent platelet clumping. Local anesthesia and sterilization were administered prior to the procedure. A total of 100 ml of bone marrow aspirate (BMA) was aspirated from the posterior iliac crest."

#### *2.1.2. Cells separation and expansion*

Under aseptic conditions in a laminar flow work area, bone marrow aspirate (BMA) was collected by puncturing the bone marrow with sterile syringes coated with

preservative-free heparin (Sigma-Aldrich, St. Louis, USA) to avoid platelet clumping. The BMA was diluted with phosphate buffer saline (PBS) and 2mM EDTA (30 ml BMA + 5ml PBS/EDTA buffer) and then carefully layered over 15 ml Ficoll Hypaque in sterile 50ml conical tubes. Mononuclear cells (MNCs) were separated by density gradient centrifugation for 35 min at 1800 rpm at room temperature. The upper layer was discarded, leaving the MNCs transferred to a new 15 ml sterile conical tube.

The cells were then washed with PBS/EDTA buffer, centrifuged for 10 min at 1800 rpm at room temperature, and suspended in 5 ml of complete media consisting of 10% fetal calf serum (FCS), penicillin (100U/ml), streptomycin (10mg/ml), and 100 µl amphotericin-B. The cells were then cultured in tissue culture flasks at a concentration of 1x106 cells/ml in a 37°C incubator with 5% CO2. After one day, non-adherent cells were discarded, and the remaining adherent cells were cultured for one week in mesenchymal media (Cambrex BioScience, Nottingham, UK), followed by three weeks in Alpha MEM media, with media changes occurring every week.

### *2.1.3. Cell harvest*

After four weeks of culture, the mesenchymal stem cells (MSCs) reaching 80-90% confluence were harvested using 0.05% trypsin and 0.53µm EDTA (GibcoBRL) prewarmed in phosphate-buffered saline (PBS) and complete media at 37°C in a water bath or incubator.

The harvested cells were suspended in 10 ml of saline and administered intravenously to the patients in a single session. Follow-up assessments were conducted three months post-transfusion in terms of clinical, laboratory, and nerve conduction studies.

### *2.1.4. Flowcytometry*

The surface expression of MSCs was evaluated using flow cytometry and a panel of monoclonal antibodies (mAbs) specific for the surface markers CD34, CD105, CD90, CD29, and CD73 (BD Biosciences, MN, USA). MSCs (1x10^6 cells) were suspended in PBS containing 1% BSA and incubated with fluorochrome-conjugated mAbs for 20 minutes at 4°C. Flow cytometric analysis was performed using a FACS Calibur instrument (BD Biosciences) and the CellQuest software. A total of 10,000 events were analyzed for each marker and a cut-off value of ≥20% was considered positive for the presence of the respective marker on the MSCs.

### *2.1.5. Immunoassay of b-FGF & VEGF by ELISA technique*

The levels of b-FGF and VEGF were quantitatively determined in all patients before and at 7 and 90 days post-transfusion of MSCs using the enzyme-linked immunosorbent assay (ELISA) technique (R&D Systems, Minneapolis, USA) according to the manufacturer's protocol. The sensitivity of the assay was determined using a Microplate Reader (Bio-Rad) at a wavelength of 450 nm.

### *2.1.6. Data analysis*

Quantitative data were represented using descriptive statistics such as mean and standard deviation (SD). The data was analyzed using appropriate statistical tests such as t-test for comparing two groups and multifactorial analysis of variance (ANOVA) for comparing more than two groups. Additionally, chi-squared test was used for analyzing qualitative data presented as numbers and percentages. Significance level of $P < 0.05$ was considered as statistically significant, while $P < 0.001$ was considered as highly significant. The statistical analysis was conducted using SPSS version 12 software.

## 3. Results and Discussion:

The present study investigated the effects of mesenchymal stem cell (MSC) transfusion in 10 diabetic patients with peripheral neuropathy (PN). Clinical, laboratory, and nerve conduction data were collected at baseline (day 0) and 90 days post-transfusion and anlaysis of B-FGF and VEGF levels at 0,7, 90 days post transfusion . Results showed that all patients exhibited improvement in at least one symptom post-transfusion. Laboratory analysis revealed significant differences in hemoglobin, glucose, and cholesterol levels at 90 days post-transfusion compared to baseline levels. Analysis of B-FGF and VEGF levels revealed a highly statistically significant difference at 7 days post-transfusion compared to baseline and 90 days post-transfusion. Immunophenotyping markers (CD105, CD90, CD29, and CD73) displayed a highly statistically significant increase in expression post-MSC culture. Nerve conduction studies revealed that most improved after MSC transfusion, with only the sural nerve amplitude showing a statistically significant difference before and after intervention. Overall, the results suggest that MSC transfusion may be a promising therapeutic option for patients with diabetic peripheral neuropathy.

The patients' clinical characteristics are showed in (Table 1). This analysis was directed on 10 diabetic patients with PN; 6 males and 4 females. Their age ranged from 33 to 45 years old, with a mean value of 41.20±4.59 years. We found that almost all patients showed improvement of one symptom or more post-MSCs transfusion. Regarding laboratory data, there was a significant statistical difference in the levels of hemoglobin, glucose (fasting and post-prandial) and cholesterol at 90 days post-MSCs transfusion (follow up period) than at day zero (baseline level) (P 0.049, 0.007, 0.005 and 0.015 respectively). Although there was no significant statistical difference in C-Peptide levels, HbA1C and creatinine (P 0.893, 0.153 and 0.128 respectively), their levels were increased in the follow-up period than at baseline level (Table 2).

Regarding B-FGF and VEGF, there was a highly statistically significant difference in their levels when measured at 7 days than at day zero and 90 days post-MSCs transfusion (P 0.001) (Table 3). Immunophenotyping markers (CD105, CD 90, CD 29 and CD73) presented a highly statistically significant difference in their expression before and after MSC culture in all patients with an increase in their levels at the end of culture ($P < 0.01$) (Table 4). CD34 surface expression did not show a significant difference before and after culture.

**Table 1.** Clinical symptoms distribution of study population before and after MSCs transfusion

| Clinical Symptoms | | Before | | After | |
|---|---|---|---|---|---|
| | I No | | 0% 100% 0% | | 40% |
| tingling and numbness | Yes | | 100% | | 60% |
| sensation burning sensation | No | 10 | 80% | 4 | 80% |
| | Yes | 1 0 | 20% | 6 8 | 20% 100% |
| ulcer or amputation | | \| 10 | 0% | 2 10 o 4 | 0% |
| | Yes | 1 8 | 100% | 6 | |
| diminished vibration sense | No | 1 2 | 0% | 6 | 60% |
| | Yes | 1 0 | 100% | 4 | 60% |
| diminished pin prick | | \| 10 | | 6 | |
| | Yes No | 1 0 | | 4 | 60% |
| diminished reflexes | Yes | \| 10 | 60% | | |
| | | 4 | | | |
| | | 6 | | | |

**Table 2.** The basic laboratory tests comparisons at baseline (day zero) and at 90 days post MSCs transfusion

| I Item uu(y/dl) | Day zero | 90 days | P value* |
|---|---|---|---|
| Fasting blood glucose (mg/dl) | 12.0± 1.6 | 12.8± 1.7 | 0.049 |
| 2 hours post prandial blood glucose (mg/dl) | 211.3±61.9 | 145.7 ± 37.6 | 0.007 |
| C-peptide (ng/ml) | 291.5 ± 106.6 | 190.3 56.4 | 0.005 |
| UWAIC (%) | 2.5 ± 1.3 | 3.1 ± 1.8 | 0.893 |
| Cholesterol (mg/dl) | | 8.0 1.9 | 0.153 |
| I Creatinine (mg/dl) | 201.2±43.7 | 185.6+32.0 | 0.015 |
| | | 1.2 ± 0.8 | 0.128 |

P value S 0.05 significant

**Table 3.** Comparison between B-FGF and VEGF levels at baseline (Day zero), 7- and 90-days post MSCs transfusion

| | Zero days | | 7 days | | 90 days | | P value* |
|---|---|---|---|---|---|---|---|
| b-FGF | 30.2 ± | 16.7 | 55.4 | 12.3 | 30.3 ± | 14.8 | |
| VEGF | 428.7 ± | 125.0 | 601.8 | 141.8 | 371.5 ± | 121.9 | **0.001** |
| | | | | | | | **0.001** |

P value S 0.05 significant

**Table 4.** Statistical comparison of CD markers percentage in all patients before and after MSCs culture

| Item (mean± SD) | I Before culture | After culture | P value* |
|---|---|---|---|
| CD 105 | 5.3 ± 0.98 | 51.8±31.7 | <0.001 |
| CD 90 | 2.9 ± 0.78 | 60.1 32.26 | <0.001 |
| CD 29 CD 73 | 3.7 1.01 | 60.28 33.09 | <0.001 |
| | 2.9±0.91 | 63.31 ± 29.52 | <0.001 |

P value S 0.05 significant

**Table 5.** Summary table showing comparison of nerves response tests at basal line (day zero) and 90 days after intervention

| Tested | nerve | Variable | On day zero mean | SD | On day 90 mean | SD | P value* |
|---|---|---|---|---|---|---|---|
| Motor nerves | Tibial nerve | Conduction velocity (m/sec) | 43.6 | 8.5 | 44.4 | 6.6 | 0.508 |
| | | Latency (msec) | 4.4 | 1.9 | 4.1 | 1.3 | 0.441 |
| | | Amplitude | 3.8 | 4.0 | 3.4 | 3.0 | 0.838 |
| | Common peroneal nerve | Conduction velocity (m/sec) | 43.8 | 10.3 | 45.2 | 12.3 | 0.575 |
| | | Latency (msec) | 4.4 | 1.8 | 4.2 | 1.1 | 0.331 |
| | | Amplitude (mV) | 2.2 | 1.9 | 2.2 | 1.2 | 0.444 |
| | Ulnar motor nerve | Conduction velocity (m/sec) | 56.0 | 8.7 | 54.2 | 10.6 | 0.721 |
| | | Latency (msec) | 2.9 | 0.8 | 2.9 | 0.7 | 0.878 |
| | | Amplitude | 5.4 | 1.9 | 6.3 | 1.8 | 0.114 |
| Sensory nerves | Ulnar sensory nerve | Conduction velocity (m/sec) | 52.0 | 16.3 | 51.2 | 12.4 | 0.721 |
| | | Latency (msec) | 3.0 | 1.0 | 2.7 | 0.8 | 0.172 |
| | Sural nerve | Amplitude (uV) | 23.1 | 16.5 | 21.3 | 11.6 | 0.878 |
| | | Conduction velocity (m/sec) | 21.1 | 22.7 | 25.5 | 27.0 | 0.080 |
| | | Latency (msec) | 2.2 | 2.4 | 2.5 | 2.8 | 0.500 |
| | | Amplitude (uV) | 5.2 | 5.8 | 7.3 | 8.6 | |
| | | | | | | | 0.043 |

P value S 0.05 significant

Compared to nerve conduction studies before and after the intervention, most nerve conduction studies improved after MSCs transfusion but were not statistically significant. Only Sural nerve amplitude showed a statistically significant difference before and after intervention (Table 5).

The current study aimed to investigate the effects of mesenchymal stem cell (MSC) transfusion on patients with diabetic peripheral neuropathy (DPN). DPN, a common complication of diabetes mellitus, is expected to affect up to 236 million people globally and poses significant challenges to healthcare systems and the general public[9]. Despite the prevalence of DPN, there are currently no conclusive treatments for the condition. Conventional therapies focus on precise glycemic management in order to limit the risk of future nerve injury and pain related to DPN[10,11]. Previous research in experimental animal models has suggested that MSCs may have potential benefits in treating DPN. However, clinical trials of MSC therapy for DPN are limited [12]. The current study sought to evaluate the impact of MSC transfusion on symptoms of DPN, including pain relief, sensory loss, and nerve conduction enhancement.

The results of the study indicate that almost all patients showed improvement in at least one symptom of DPN following MSC transfusion. These findings are consistent with previous research[13,14], which has suggested that MSC transfusion may be effective in managing intractable pain and improving neurological function through neurorestorative mechanisms, including neuroconstructive interventions, immunomodulation, and microcirculation enhancement. Additionally, two patients with diabetic foot ulcers, one of whom was facing amputation of the little toe, showed dramatic improvement following MSC transfusion. This is in line with previous research which has demonstrated that MSCs can accelerate wound closure,

improve clinical parameters, and avoid amputation through their paracrine effects on migration, angiogenesis, and re epithelialization [15,16].

In addition to evaluating clinical symptoms, the study also assessed laboratory test results at baseline and 90 days post-MSC transfusion. The results showed a significant improvement in levels of hemoglobin, fasting and post-prandial glucose, and cholesterol at the 90-day follow-up period compared to baseline. The present study aimed to evaluate the effect of mesenchymal stem cell (MSC) transplantation on glucose homeostasis and angiogenesis in diabetic rats. A follow-up period was conducted and levels of c-peptide, HbA1c, and creatinine were measured at baseline and at the end of the follow-up period. Although no significant statistical difference was observed in these parameters (P values of 0.893, 0.153, and 0.128 respectively), it was observed that their scores improved in the follow-up period compared to the baseline level. This finding is consistent with previous studies, such as Si et al., 2012[17], who found that MSC transplants reduced blood glucose levels in diabetic rats.

Additionally, the levels of serum b-FGF and VEGF were measured at 7 and 90 days post-MSC infusion and compared to basal levels. The highest level was observed at 7 days, with a significant difference compared to levels measured at day zero and 90 days (P value of 0.001). These results align with previous studies, such as Kwon et al., 2014[18] who found that MSCs can enhance angiogenesis through direct translation, cell-cell communication, or signaling cascade. Furthermore, Shibata et al., 2010 revealed that VEGF and b-FGF mRNA expression were considerably elevated in MSC-injected thigh muscles of STZ-induced diabetic rats, further supporting our findings. Overall, this study suggests that MSC transplantation may improve glucose homeostasis and enhance angiogenesis in diabetic rats

In our study, we aimed to investigate the effect of mesenchymal stem cell (MSC) transfusion on nerve conduction studies by comparing results obtained before and after the intervention. Our results showed that most nerve conduction studies improved after MSC transfusion, but these improvements were not statistically significant. The exception was the sural nerve amplitude, which exhibited a statistically significant improvement post-intervention. This finding is in agreement with previous research by Han et al. (2016)[19], who evaluated the potential of local MSC implantation to enhance diabetic neuropathy by promoting angiogenesis and neuronal regeneration, such as remyelination. The study by Han et al. revealed that motor and sensory nerve conduction velocities (NCVs) and capillary density were decreased in the sciatic nerves of streptozotocin (STZ)-induced diabetic rats, but recovered to relatively close levels after the intervention. These observations suggest that the improvement in nerve amplitude may be due to the emergence of novel links between surviving undamaged axons and muscle fibers that have lost their innervation, rather than an improvement in nerve velocity.

This hypothesis is supported by evidence that the first function to be improved after regeneration is amplitude, while velocity may reduce first and then increase with longer duration. In cases of generalized neuropathy where the destruction of axons is weak, the surviving undamaged axons may have enough time to form new connections to muscle fibers that have lost their innervation (collateral re-innervation). The compound muscle action potential (CMAP) could remain within the regular magnitude spectrum, but the maximum count of nerve axons is fewer. However, due to the influence of the short internodal intervals, the immature regenerating fibers have lower velocity, resulting in a more distributed CMAP.

## 4. Conclusion

In conclusion, our study suggests that MSC transfusion may be a promising therapeutic strategy for diabetic patients to improve their overall health by controlling blood sugar levels, reducing insulin requirements, and ameliorating complications such as peripheral neuropathy. This is likely due to the paracrine effects of MSCs, which involve the secretion of b-FGF and VEGF, which have been shown to have angiogenic and neurosupportive effects. However, further research is needed to optimize the dose, number of sessions, and transfusion method for optimal efficacy. It is also important to note that our study focused on evaluating the effect of MSC transfusion on nerve conduction studies and more research is needed to evaluate the effect of MSC transfusion on other diabetic complications.

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## Disclosure

There are no conflicts of interest to declare.

## Ethical approval

All protocols involving human subjects in this research were carried out to comply with the Helsinki Declaration's ethical principles. The study was approved by National Cancer Institute, Cairo University MD20100-14011.

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