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Commentary: Transplantation of Dental Pulp Stem Cells Improves Long-Term Diabetic Polyneuropathy together with Improvement of Nerve Morphometrical Evaluation

Keiko Naruse

Department of Internal Medicine, School of Dentistry, Aichi Gakuin University, Japan

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***Correspondence:**

Dr. Keiko Naruse, Department of Internal Medicine, School of Dentistry, Aichi Gakuin University, 2-11 Suemori-dori, Chikusa-ku, Naogya 464-8651, Japan; Telephone No: +81-52-759-2307; FAX No: +81-52-759-2168; E-mail: narusek@dpc.agu.ac.jp.

Diabetic neuropathy is the most common diabetic complication and occurs from the early phase of diabetes, sometimes from the phase of impaired glucose tolerance[1]. The onset and progression of diabetic neuropathy are fundamentally linked to metabolic disorders and blood flow impediments resulting from chronic hyperglycemia, with immunological dysfunction and aging as additional contributing factors. The symptoms of diabetic neuropathy are varied and impair quality of life[2]. Furthermore, the presence of diabetic neuropathy associates with mortality[3]. Although blood glucose control reduces the onset and progression of diabetic neuropathy, sometimes it is not enough for amelioration[4]. There are drugs which reduce the pain-related symptoms. However, the final goal of the treatment with diabetic neuropathy is to improve nerve function and pathological abnormalities with the management of the neuropathic pain[5-7]. Therefore, more fundamental treatments for diabetic neuropathy are needed.

Our study, entitled "Transplantation of dental pulp stem cells improves long-term diabetic polyneuropathy together with improvement of nerve morphometrical evaluation" has revealed a promising effects of dental pulp stem cell(DPSC) transplantation on diabetic polyneuropathy with a long duration of diabetes[8]. Rats with 52-week duration of diabetes exhibited reductions in the sciatic motor/sensory nerve conduction velocity, nerve blood flow, and intraepidermal nerve fiber density and increases in the current perception threshold in the peripheral nerves. All of which were ameliorated by DPSC transplantation into the hindlimb skeletal muscles.

Cell transplantation using cultured endothelial progenitor cells (EPCs) and mesenchymal stem cells (MSCs), including dental pulp stem cells (DPSCs), ameliorated nerve conduction velocity, nerve blood flow, and intraepidermal nerve fiber density in diabetic animals[9-13]. However, since most previous studies were of relatively short duration; 2-16weeks, the morphology in sural nerves did not differ between normal and diabetic animals, except axonal circularity[10, 14]. To conquer this problem, we harvested long-term (52-week) diabetic rats with low-dose administration of insulin. Our study was the first study which evaluated the effects of stem cell transplantation in animals with a long-term diabetes.

The morphological characteristics of diabetic polyneuropathy include axonal atrophy, nerve demyelination, and reduced regeneration of peripheral sensory nerve fibers[15]. In sural nerve biopsies from patients with mild diabetic neuropathy, teased fiber studies revealed paranodal abnormalities, segmental demyelination and remyelination

without axonal degeneration, suggesting that Schwann cell abnormalities precede axonal degeneration[16]. Decreases in myelinated fiber density and occupancy were observed in both large and small fibers as the disease progressed[17, 18]. The long-term diabetic rats in our study demonstrated decreases in the fiber area, occupancy rate, myelin area, and myelin thickness, and an increase in the axonal-to-myelin area ratio, compared with those in the normal rats, suggesting that our long-term diabetic rat model mimics from mild to middle stage of diabetic polyneuropathy in human. The transplantation of DPSCs significantly increased the myelin thickness and area, indicating that the transplantation of DPSCs affected myelin formation in the sural nerve morphology.

Proliferation of rat Schwannoma cells significantly suppressed by polyol pathway activation induced by high glucose condition[19]. Cultured Schwann cells from both type 1 and type 2 diabetic mice showed lower production of Nerve growth factor (NGF) and Neurotrophin-3(NT-3) compared to cultured Schwann cells from normal mice[20]. We previously revealed that high glucose significantly reduced NGF secretion from cultured mouse Schwann cells, which reduced the response on neurite outgrowth[21]. Using rodent Schwann cell culture, we confirmed the effects of DPSC-secreted factors on the proliferation and production of myelin-related protein in Schwann cells. Since Schwann cells maintain peripheral nerve structure and function by ensheathment of unmyelinated axons, myelination of myelinated axons, and secretion of neurotrophic factors[22-24], the impact of DPSC transplantation on Schwann cells is crucial for the improvement of diabetic polyneuropathy.

We supposed several therapeutic mechanisms of the DPSC transplantation for diabetic polyneuropathy. The First is neurotrophic effect. Transplantation of DPSCs improved intraepidermal nerve fiver density and myelin thickness in sural nerves of diabetic rats. The second is immunomodulatory effect. DPSC-secreted factors promote macrophages polarization towards anti-inflammatory M2 phenotypes, which result in the suppression of inflammation in the peripheral nerve of diabetic polyneuropathy[14]. The third is vasculogenic/angiogenic effect. Some of the transplanted DPSCs still existed in the transplanted site and differentiated into vascular endothelial cells, suggesting that transplanted DPSCs cooperated with the resident cells and induced vasculogenesis[13]. In addition, since DPSC-secreted factors include abundant angiogenic factors, the proliferation of residual endothelial cells may be increased by DPSC transplantation. Transplantation of DPSCs increased capillary/muscle ratio in the skeletal muscles of diabetic rats and increased sciatic nerve blood flow.

On the other hand, the therapeutic efficacy of stem cells was impaired by diabetic condition or aging[25, 26]. To avoid these problems, DPSC is an attractive candidate for cell therapy because these are easy to obtain from teeth extracted at an early age by orthodontic reasons without further invasive procedures. Furthermore, the obtained DPSCs may be stem cells before the onset of diabetes. DPSCs can be cryopreserved until they are needed[13]. Allograft is another option. Since most animal experiments in our studies and other studies were allograft, the efficacy of allograft using DPSCs has already been proved. If we can stock DPSCs from many adolescents, DPSCs with less mismached human leukocyte antigens (HLAs) may be found and used for allograft.

DPSC-secreted factors play a crucial role in DPSC transplantation. The administration of DPSC-conditioned media (DPSC-CM) improved diabetic polyneuropathy[27]. The therapeutic efficacy of DPSC-CM administration in diabetic polyneuropathy was almost comparable to those of DPSC transplantation. However, the effect of DPSC-CM for motor nerve conduction velocity was lower than that of DPSC transplantation. Furthermore, only DPSC transplantation proved the effects to long-term diabetic polyneuropathy, at present. These results suggest that the application of DPSC transplantation or DPSC-CM administration should be selected depends on the clinical stage of diabetic polyneuropathy. Taken together, DPSC transplantation on diabetic polyneuropathy will provide insights into novel therapeutic strategies for patients with all ages.

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