# Alteration of Sciatic Nerve Histology and Electrical Function After Compression and After Neurolysis in a Diabetic Rat Model

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**Background:** Diabetic rats are more sensitive to nerve entrapment. This study was conducted to evaluate nerve function and histological changes in diabetic rats after nerve compression and subsequent decompression.

**Methods:** A total of 35 Wistar rats were included. The experimental group was divided into diabetic sciatic nerve compression group (DSNC, n = 5) and diabetic sciatic nerve decompression group (DSND, n = 20). The DSNC model was created by wrapping a silicone tube circumferentially around the nerve for 4 weeks, and then the DSND group accepted nerve decompression and was followed up to 12 weeks. The DSND group was equally divided into DSND 3 weeks (DSND3), 6 weeks (DSND6), 9 weeks (DSND9), and 12 weeks (DSND12) groups. Five rats were taken as normoglycemic control group (CR, n = 5), and another 5 rats as diabetic control group (DM, n = 5). The mechanical hyperalgesia of rats was detected by Semmes-Weinstein nylon monofilaments (SWMs) and by motor nerve conduction velocity (MNCV). These 2 physiological indicators and histology of sciatic nerves were compared among different groups.

**Results:** The SWM measurements improved toward normal values after decompression. The SWM value was significantly lower (more normal) in the DSNC groups than in the DSND group ($P < 0.05$). The MNCV was 53.7 ± 0.8 m/s in the CR group, whereas it was 28.4 ± 1.0 m/s in the DSNC group ($P < 0.001$). Six weeks after decompression, the MNCV was significantly faster than that in the DSNC group ($P < 0.001$). Histological examination demonstrated chronic nerve compression, which responded toward normal after decompression, but with degree of myelination never recovering to normal.

**Conclusions:** Chronic compression of the diabetic sciatic nerve has measureable negative effects on sciatic nerve motor nerve function, associated with a decline of touch/pressure threshold and degeneration of myelin sheath and axon. Nerve decompression surgery can reverse these effects and partially restore nerve function.

**Key Words:** decompression, diabetes, neurolysis, sciatic nerve

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Diabetic peripheral neuropathy (DPN) is one of the most common and intractable chronic complications of diabetes mellitus.[1] In patients with diabetes for 20 years, the incidence of DPN is up to 50%.[2] Diabetic peripheral neuropathy is partially caused by swelling of nerves, which are subjected to entrapment at the sites of anatomical stenosis.[3] A hypothesis of the "double crush syndrome" was outlined in 1973.[4] This concept proposes that a nerve affected by metabolic disease or compressed at a proximal site would be more susceptible to compression at a distal potential entrapment site. Experimentally, in rat models, the peripheral nerve in the presence of diabetes was proved more susceptible to chronic compression than in the nondiabetic rat.[5]

In 1992, in the first report of peripheral nerve decompression applied to treatment of DPN reported by Dellon,[6] 85% of all the patients obtained improvement in sensory and motor symptoms. Since then, an increasing number of studies have reported promising results. Pain relief and sensory recovery were obtained in approximately 80% of DPN patients after decompression of peripheral nerves in the lower limb.[7,8] In addition, incidence of ulceration and amputation was also significantly decreased.[9] Trignano et al[10] presented that decompression not only restored nerve function, but also increased the microcirculation in the feet of diabetic patients.

The purposes of this study were to establish the nerve compression model of streptozotocin (STZ)–induced diabetic rat and to compare the index of mechanical sensory threshold, electromyography, and the change of histology in diabetic rats before and after decompression, in order to provide further basis for understanding the clinical treatment of peripheral neuropathy in diabetes.

## METHODS

Thirty-five male Wistar rats weighing approximately 250 g were used in this study. All experimental procedures involving animals were approved by the Institutional Animal Care and Use Committee of Fudan University. Every measure was taken to minimize the number of animals and minimize their discomfort. Before experiments, all animals were adapted to the specific pathogen-free experimental circumstance for 7 days. To create the diabetic model,[11] rats were given a single intraperitoneal injection of STZ 60 mg/kg. Blood samples were collected through tail vein and measured with a glucometer 2 weeks later. Rats with random blood glucose values higher than 16.6 mmol/L were further assigned to diabetic experimental groups. Preparation for diabetic rats did not end until diabetes was successfully induced in 30 rats. Nondiabetic rats were used as the control group. When the experiment finished, the animals were killed by overdose of anesthetics.

### Diabetic Sciatic Nerve Compression Group Model Establishment

The rats were anaesthetized by intraperitoneal injection of 40 mg/kg pentobarbital. After anesthesia administration, each rat was placed in ventral position with an exposed right lower limb.[5] The anatomical reference points for the sciatic nerve were the sciatic notch and the femur. The rats were operated on special animal operation room with aseptic conditions, and their skin was wiped with 75% alcohol for 3 times before the operation. The sciatic nerve was defined by splitting the biceps femoris muscle fibers after incision of skin and was exposed about 1.5 cm. Once the sciatic nerve was identified and dissected, a 1-cm silicone tube was wrapped circumferentially around the middle third of the nerve and fastened with 8-0 nylon sutures[12,13] (Fig. 1). When the sciatic nerve was compressed, a microscope was used to ensure that the pressure

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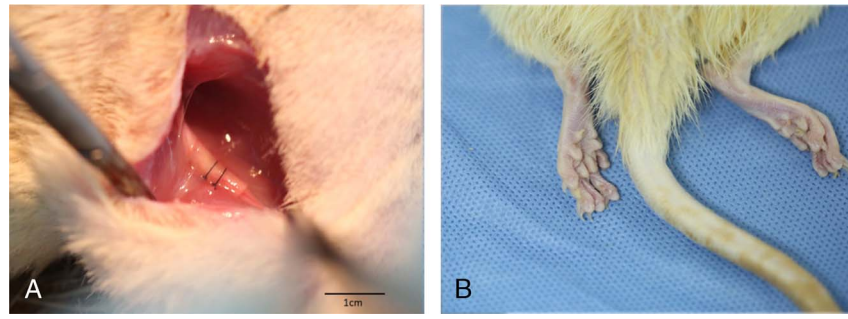


**FIGURE 1.** A, Sciatic nerve compression process. It can be seen that the surface of nerve was smooth, and the sciatic nerve of rat was compressed by a silicone tube with silk ligation. B, Local changes of rats after compression The hair of diabetic rat turned yellow, and the plantar of compression side was contractural.

is appropriate. The silicone tubes with length of 1.0 cm and diameter of 1.2 mm were utilized. When it was used to compress the sciatic nerve, a silicone tube should not be overlapped or leave any space between 2 borders. The silicone tube was ligated to avoid sliding and acute nerve degeneration. All the procedures were performed by the same individual to exclude interoperator influence.

## Experimental Design

Five Wistar rats were taken as nondiabetic control group (CR group, n = 5). Thirty diabetic rats were randomly divided into diabetes mellitus group (DM, n = 5), diabetic sciatic nerve compression group (DSNC, n = 5), and diabetic sciatic nerve decompression group (DSND, n = 20). The DM group was without any surgery intervention, whereas the DSNC and DSND groups were made as sciatic nerve compression models. Four weeks later, the DSND group rats were subjected to sciatic nerve decompression. According to the different periods after decompression, the DSND group was divided into DSND 3-week group (DSND3), DSND 6-week group (DSND6), DSND 9-week group (DSND9), and DSND 12-week group (DSND12), with each group consisting of 5 rats. The mechanical algesia, electrophysiology, and histology in sciatic nerves of each group were examined.

## Touch/Pressure Measurement

The touch/pressure "threshold" of the right foot with sciatic nerve compression was measured after 4 weeks and compared with that in the CR group. Positive touch/pressure perception and visible foot muscle contracture indicated successful modeling. Then, 20 rats were prepared for the decompression surgery as the DSND group. The silicone tube was removed from the sciatic nerve through the original surgical path. In addition, the adhesion tissue around the sciatic nerve was released, completing the neurolysis of the sciatic nerve (Fig. 2).

## Sensory Behavioral Determination

The rats were placed in a transparent container and adapted for 30 minutes. The plantar aspect of their right hindfoot was stimulated with different types of Semmes-Weinstein nylon monofilament (SWM) to determine their reaction. Rat hindfoot lifting, jittering, delayed releasing, or escaping was considered as positive for perception of the touch/pressure stimulus. The minimum numerical value of the aforesaid situation was recorded as the filament marking.

## Electrophysiological Testing of Nerve

The sciatic nerve was exposed in the anesthesia situation; a bipolar electrode as the stimulus electrode was directly placed on the sciatic nerve, and a single pole needle electrode was inserted into the ipsilateral gastrocnemius muscle as the upper part of the recording electrode, whereas another unipolar needle electrode into the tendon. The ground electrode was fixed in the rat tail. After adjusting the stimulation current into 0.6 mA and the stimulation frequency into 0.5 Hz, the proximal and the distal stimulations were carried out. respectively. Conduction velocity was calculated using the difference between proximal and distal latencies together with the distance between proximal and distal stimulation sites.[14] Then motor nerve conduction velocity (MNCV) was recorded: MNCV = distance between stimulation sites/latency.

## Histological Analysis

Approximately 1 cm sciatic nerve under the silicone tube was harvested with microinstruments for analysis. Then the sciatic nerve was fixed with 4% paraformaldehyde to make paraffin sections. Routine hematoxylin-eosin stain and immunofluorescence were performed to observe the histopathologic changes of the nerve tissue in different groups. The sections were immunostained using anti-S100 antibody (ab34686; Abcam, United Kingdom) to show Schwann cells (SCs) at

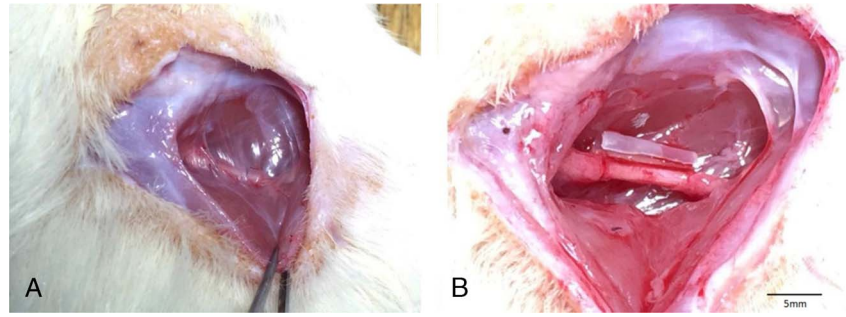


**FIGURE 2.** A, Decompression surgical approach. Sciatic nerve was exposed along the original surgical incision in diabetic rat. B, Release the sciatic nerve of rat silicone tube, and adhesion tissue around the nerve should be removed together.

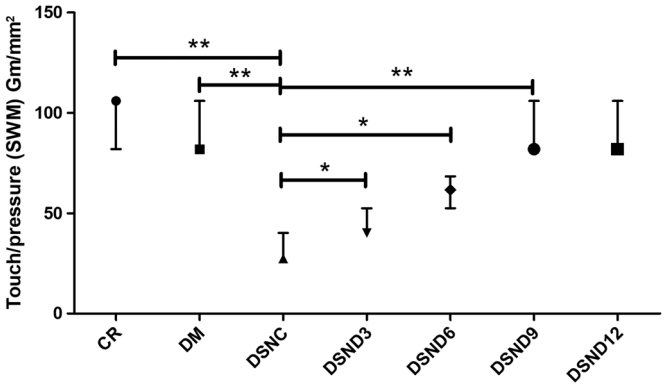


**FIGURE 3.** Compared with other groups, the SWM touch/pressure of the rats in the DSNC group was significantly lower ($P < 0.05$). The touch/pressure was gradually increased to a stable level with the prolongation of the decompression time. The touch/pressure at the DSND9 group was higher than that at the DSND6 group. Even though touch/pressure in the DSND9 and DSND12 groups was lower than that in the CR group, there was no significant difference between them. $*P < 0.05$, $**P < 0.01$.

4°C overnight after having been blocked by 5% milk in Tris-buffered saline for 30 minutes.[15,16] Sections were subsequently washed in Tris-buffered saline for 3 times and then exposed to anti–rabbit secondary antibody (Guge Biology Technology Company, Wuhan, China) for 60 minutes.

### Statistical Analysis

Data were compiled by SPSS 20.0 software (International Business Machines Corp, Armonk, NY) and GraphPad Prism 5 (GraphPad Software, La Jolla, CA). The normally distributed data were presented as mean ± SD, and non–normally distributed data were shown as median and range. Comparisons between groups of normally distributed variables (MNCV) were performed by 2-sample *t* tests. Mann-Whitney *U* tests were utilized to compare intergroup difference of non–normally distributed variables (SWM touch/pressure). Differences were considered significant if $P < 0.05$. The SWM marking is the force in 0.1 mg, which is then divided by the cross-sectional area to determine the pressure applied. It is this measurement, and not the monofilament marking itself, that was used for the statistical comparison.[17]

## RESULTS

The SWM touch/pressure was measured in different groups. The SWM pressure of the CR group was 106 g/mm$^2$ (82.0–106 g/mm$^2$), and the DM group was 82.0 g/mm$^2$ (82.0–106 g/mm$^2$), but the outcome was significantly reduced to 27.4 g/mm$^2$ (27.4–40.3 g/mm$^2$) after compression ($P < 0.01$). With prolongation of the period after decompression, the touch/pressure gradually increased. The value was 40.3 g/mm$^2$ (40.3–52.6 g/mm$^2$) in the DSND3 group ($P < 0.05$) and 61.7 g/mm$^2$ (52.6–68.3 g/mm$^2$) in the DSND6 group ($P < 0.05$), which were statistically higher than that in the DSNC group. The figure was 82.0 g/mm$^2$ (82.0–106 g/mm$^2$) in the DSND9 and the DSND12 groups. Even though they had a decreased touch/pressure compared with the CR group, there were no significant differences between them (Fig. 3).

The MNCV was 53.7 ± 0.8 m/s in the CR group and 48.7 ± 0.9 m/s in the DM group. The MNCV of the DSNC group was 28.4 ± 1.0 m/s, which was significantly slower compared with other groups ($P < 0.001$). However, the numerical value at the DSND3 group had no difference compared with the DSNC group, approximately 30.7 ± 1.5 m/s. At 6 weeks, the significant difference began to show up with the MNCV, about 38.6 ± 1.0 m/s ($P < 0.001$). The MNCVs of sciatic nerve were gradually restored with the prolongation of the decompression time. The figure was 43.3 ± 1.1 m/s in the DSND9 group, and it was similar to the DSND12 group, whose MNCV was 44.5 ± 1.1 m/s. Although the recovery of nerve conduction velocity at the 12th week was similar to that of diabetic rats, it did not restore to normal condition ($P < 0.001$). There was significant difference in the nerve conduction velocity between the DM group and the CR group, with lower nerve conduction velocity in the DM group ($P < 0.01$) (Fig. 4).

Hematoxylin-eosin staining showed that the normal nerve structure was altered in the DSNC group. Nerve swelling, neuronal vacuolation, and nerve myelin and axonal degeneration could be observed (Fig. 5). Compared with the CR group, the sciatic nerve was also swollen in the DM group. At the third week after decompression, the myelin regeneration was not obvious, and extensive nerve damage was still visible. However, at the end of the sixth week, there was plenty of regenerated myelin wrapping axons, and the morphology of nerve partially returned to normal. In the DSND9 and DSND12 groups, neural morphology recovered increasingly better, with visible vascular proliferation (Fig. 6). Immunofluorescence staining showed SCs increased significantly in the DSNC group compared with the other groups. With the prolongation of period after decompression, the nerve morphology restored, SCs decreased, and axons as well as myelin regenerated gradually. In 12 weeks, the expression of SCs and regeneration of myelin compared with 9 weeks did not change a lot (Fig. 7).

## DISCUSSION

In this study, we used the Dellon model because chronic compression by banding the sciatic nerve with a silicone tube in STZ-induced diabetic rats was susceptible to compression when compared with nonbanded diabetic rats or banded nondiabetic rats.[5,12,13,18] We choose 4 weeks as the time to decompression, because serious nerve injuries and nerve function are affected significantly then.[19,20] In our compression animal model, decreased pain threshold and nerve conduction velocity were evident. After the compression in diabetic rats, the pain threshold decreased, and the nerve conduction velocity was

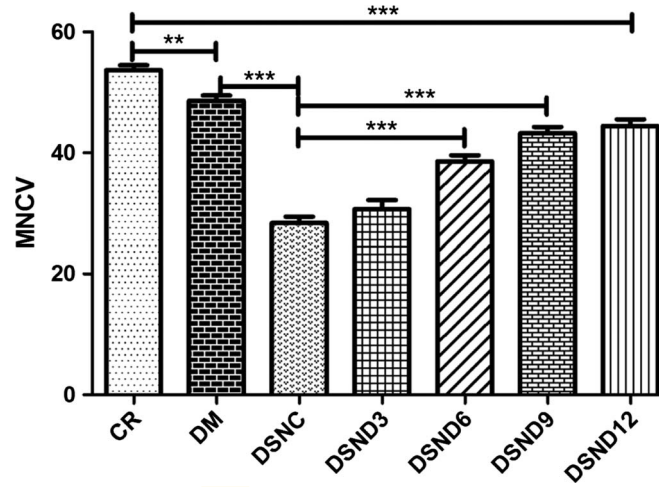


**FIGURE 4.** The MNCV of the rats in the DSNC group was significantly lower than that in other groups except DSND3 ($P < 0.001$). The nerve conduction velocity of the sciatic nerve was obviously recovered at the sixth week and gradually restored with the prolongation of the decompression time. Although the recovery of nerve conduction velocity at DSND12 was similar to that of diabetic rats, it still did not restore rats to normal. $**P < 0.01$, $***P < 0.001$.

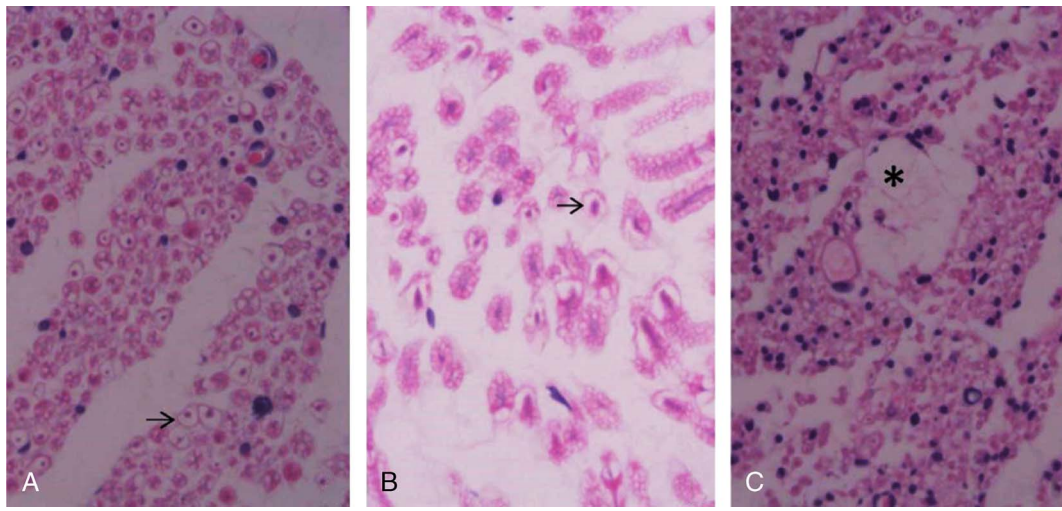


**FIGURE 5.** Normal myelin and axon structures (→) were observed in CR (A) and DM (B) groups, and the rat sciatic nerve in the DSNC group (C) turned into Wallerian degeneration (*), normal structure of myelin and axon disappeared, and nerve tissue vacuolization formed (hematoxylin-eosin stain, original magnification ×400).

down to a lower level. The histological examination of DSNC morphology showed that the nerve was grossly injured, and the normal neuronal structure disappeared, producing Wallerian degeneration.

There was no apparent recovery of nerve tissue even 3 weeks after decompression. At the sixth week, the myelin sheath presented regeneration in tissue sections. Schwann cells increased when the sciatic nerve of diabetic rat was entrapped. Along with the prolongation of decompression time and remyelination of sciatic nerve, expression of SCs also declined. The sensory of rats and nerve conduction velocity gradually increased after the decompression procedure. In the DSND12 group, the pressure and nerve conduction velocity of the rats were similar to the DM group, whereas there was still a certain gap with the CR group.

Pettersson et al[19] suggested that even a short period of compression was capable of inducing a severe effect on the nerve tissue and the nerve morphology, and signs of nerve degeneration were still present at the eighth week after decompression treatment. In our study, we extended the entire release period to 12 weeks. However, even after 12 weeks of decompression surgery, the neurological function was not restored to normal condition. Hyperglycemia leads to an excess of intramitochondrial radical oxygen species, inflammatory reactions, and edema formation in peripheral nerves.[21] Abnormal lipid metabolism can also lead to neurological changes,[22] and the increase in free fatty acids would initiate the inflammatory signaling pathway and promote the occurrence of DPN.[23] High glucose and other metabolic abnormalities lead to the accumulation of unfolded or misfolded proteins in the endoplasmic reticulum and the destruction of calcium homeostasis in nerve cells, which will trigger their apoptosis.[24] These processes, together with disturbed blood flow caused by microangiopathy, ultimately result in nerve damage.[25] It seems that neuropathy is not a single continuous process, but interaction of many factors. Kennedy and Zochodne[26] found that recovered mice had the recovery of axonal structural abnormalities but no recovery of lost neurons. Even though there was a certain gap between the

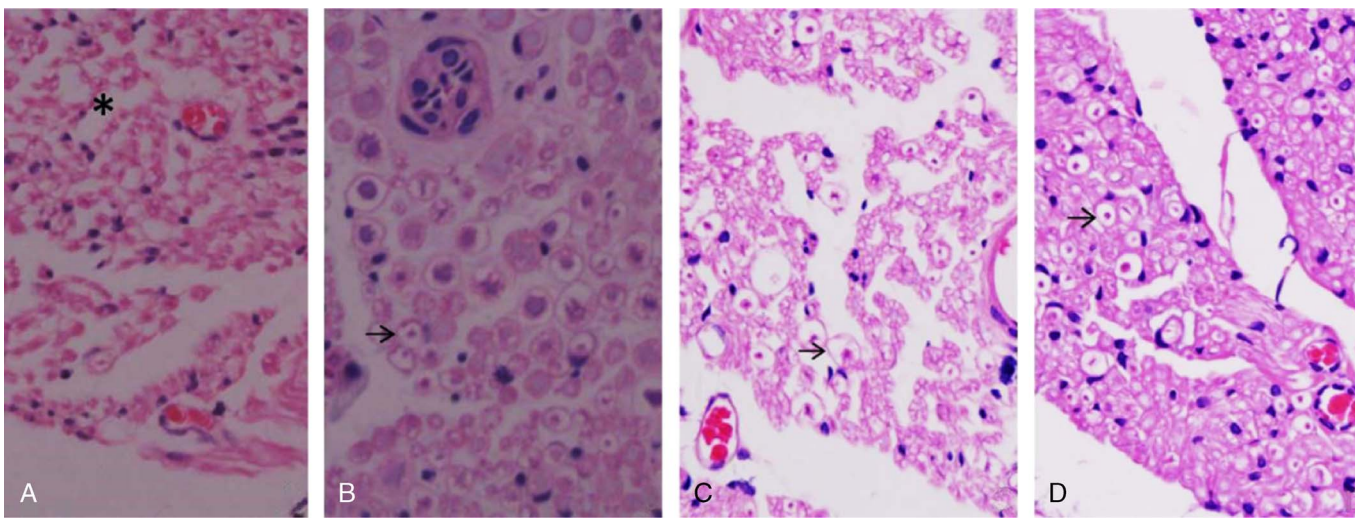


**FIGURE 6.** The sciatic nerve of rats was gradually restored with the prolongation of time. A, In the DSND3 group, the recovery of sciatic nerve was not obvious; vacuolization and demyelination (*) were serious in the nerve tissue. B, In the DSND6 group, myelin and axon regeneration (→) can be seen, and the nerve gradually returned to normal structure. C and D, The sciatic nerve recovered further in the DSND9 and DSND12 groups (hematoxylin-eosin stain, original magnification ×400).

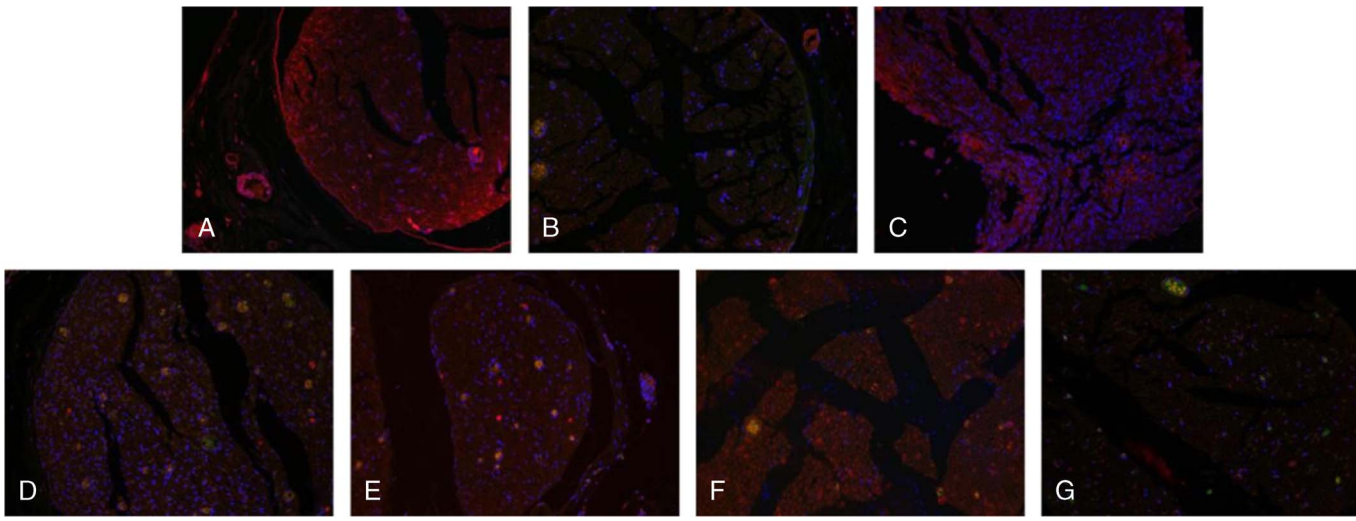


**FIGURE 7.** The expression of SCs in the DSNC group (C) was higher than that in the CR (A) and DM (B) groups. Schwann cells in sciatic nerve gradually restored, and their expression decreased gently along with the prolongation of decompression time (D–G), and it was similar to that of diabetic rats in the DSND9 (F) and DSND12 groups (G) (S100, original magnification ×200).

decompression rats and the control rats, there was no significant difference compared with the diabetic group. The indexes of decompression were highly improved than those of the compression group.

Schwann cells are differentiated from neural crest cells, and they are the most common glial cells in the peripheral nervous system. Schwann cells are essential to support neurons and nerve structure, which can synthesize and secrete various neurotrophic factors, and produce a variety of extracellular matrix for myelin formation.[27] In pathological condition, SCs can promote regeneration of axon and myelination.[28] It was the compression that caused peripheral nerve injury, then it resulted in the proliferation of SCs to repair peripheral nerve.[29] In our experiment, it was visible that the CR group rats had normal morphology and normal expression of SCs, whereas in the DSNC group, the sciatic nerve morphology was injured seriously, and SCs proliferated significantly. This was because the damage caused the proliferation of SCs. Gupta and Steward[30] showed chronic nerve compression disrupted myelin but also produced marked proliferation of SCss. Wagner and Myers[31] reported that few SCs were immunoreactive for tumor necrosis factor in the uninjured sciatic nerve, but the number of immunoreactive cells in the nerve fascicle was increased following a compression injury. Nerve compression was also proved to induce higher expression of activating transcription factor 3 in SCs in diabetic rats.[32] However, Zhong et al[33] found that distribution of SCs decreased in the DPN group, which is discrepant to other findings. That is maybe because they observed SCs relatively later than other studies after sciatic compression (>12 weeks). Besides, they used electron microscopy to calculate SCs with a high magnification (×2000), which probably could focus on only a small part, other than the whole situation of the nerve. In the repair of injured nerves, SCs degrade 40% to 50% of the myelin debris within the first phase through autophagy, and the remaining myelin debris is cleared primarily by macrophage-mediated phagocytosis in the later phase.[34,35] As shown by our experimental results, myelin and neuronal function gradually recovered, and SCs also showed decreased trend with prolonged decompression time.

Nowadays, SCs have been utilized for peripheral nerve repair and transplantation.[36,37] Several previous studies also demonstrated that using transplantation of SCs to treat spinal cord injuries was promising.[38–40] However, it was found that activity of SCs was suppressed because of excessive proliferation of glial cells in the nerve scar.[41] Reactive astrocytes, meningeal cells, and microglia contribute to formation of the glial scar after damage to spinal cord around the lesion site, which is both a structural and chemical barrier to axon growth.[42] The cellular components of the glial scar express axonal growth inhibitory molecules such as chondroitin sulfate proteoglycans (CSPGs) by astrocytes.[41,43] Schwann cell transplantation after spinal cord injury was observed to increase CSPG intensity at the interfaces.[42] Degradation of CSPGs by the chondroitinase ABC enzyme removed a regeneration barrier from the glial scar and enhanced plasticity in the spinal cord by removing perineuronal nets.[44] In addition, increase in the level of cyclic adenosine monophosphate together with an SC graft within a contused spinal cord promoted the axonal growth response and functional recovery.[45] In consequence, the transplantation of SCs needs to be combined with other strategies, focusing on those aspects of nerve repair that are not obtained by SCs grafting alone. Using SC transplantation combined with interventions to suppress glial scar–induced inhibition might open new therapeutic avenues on nerve regeneration. Because of the important role of SCs as neural regeneration and functional support cells, they may have high probability to be applied for the treatment of DPN in the future.

Siemionow et al[46] decompressed peroneal nerve and tibial nerve at 2 potential entrapment sites of Zucker diabetic fatty rats at the onset of diabetes before the neuropathy was established. Similarly, Kale et al[47] decompressed perineural sheaths, exposed through the epineurotomy sites on both the peroneal and tibial nerves of Sprague-Dawley rats with STZ injection prior to the occurrence of DPN. They all utilized Walking Track Analysis to observe the behavior of rats, but not the threshold of pain. The sciatic function indexes and somatosensory-evoked potentials were improved on the surgical nerve release sides compared with the other side in Siemionow and colleagues'[46] experiment, but they did not observe histological changes of the nerves. Although Kale and colleagues[47] observed the morphology of myelin, they ignored the role of SCs. Both studies demonstrated that decompression surgery could prevent deterioration in the neurological function of DM rats, even though DPN has not happened, which added to evidence that peripheral nerve entrapment had a significant impact on the development of DPN. However, it seems unreasonable to conduct decompression surgery on all the DM patients without considering the occurrence of DPN.

In an earlier experiment, Walker et al[48] concluded that there were no detectable structural abnormalities or early functional abnormalities in the peripheral nerves of the STZ-induced diabetic rats. Therefore, in this experiment, silicone tubes were utilized to create rat sciatic nerve compression, a simulation of clinical peripheral nerve entrapment, instead of waiting for the diabetic rats to develop peripheral neuropathy.

We used the method of combining macroscopic and microscopic analyses to compare the changes of rats with diabetes mellitus before and after the neurolysis in sciatic nerves, and the most important was that we observed the effect of decompression on sciatic nerve at different points in time after the surgery.

## CONCLUSIONS

This study demonstrated that chronic sciatic nerve compression of the diabetic Wistar rats caused neurophysiological and histological changes. In the meantime, decompression of the sciatic nerve would result in partial recovery of the nerve function and morphology.

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