

Diabetic Peripheral Neuropathy Increases Electrical Stimulation Threshold of Sciatic Nerve: A Prospective Parallel Cohort Study

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Purpose: To investigate the impact of diabetic peripheral neuropathy and its severity on the threshold of sciatic nerve electrical stimulation in diabetic patients.

Patients and Methods: The case-control study included 60 patients that were divided into non-diabetic patients (control group, $n = 26$) and diabetic patients (diabetes group, $n = 34$). All the patients who were scheduled for lower leg, foot, and ankle surgery received a popliteal sciatic nerve block. We recorded the minimum current required to produce motor activity of the sciatic nerve during ultrasound-guided popliteal sciatic nerve block.

Results: Among the 60 patients, the sciatic nerve innervated muscle contractile response was successfully elicited in 57 patients (dorsiflexion of foot, plantar flexion, foot valgus or adduction, toe flexion, etc.) under electric stimulation. We failed to elicit the motor response in three patients with diabetic peripheral neuropathy, even when the stimulation current was 3 mA. The average electrical stimulation threshold (1.0 ± 0.7 mA) in the diabetes group was significantly higher than that of the control group (0.4 ± 0.1 mA). Diabetic patients with peripheral neuropathy had a higher electrical stimulation threshold (1.2 ± 0.7 mA) than patients without peripheral neuropathy (0.4 ± 0.1 mA). Furthermore, the electrical stimulation threshold of the sciatic nerve in diabetic patients had a linear dependence on the Toronto Clinical Scoring System (TCSS) peripheral neuropathy score (electrical stimulation threshold [in mA] = 0.125 TCSS score) ($P < 0.001$).

Conclusion: The threshold of electrical stimulation to elicit a motor response of the sciatic nerve was increased in diabetic patients, and the threshold of electrical stimulation of the sciatic nerve increased with the severity of diabetic nerve dysfunction.

Keywords: diabetes mellitus, peripheral neuropathy, electrical stimulation threshold, nerve block

Introduction

Diabetes mellitus is one of the most common chronic diseases. It threatens the lives and health of people and imposes a huge social, financial, and health burden globally. The International Diabetes Federation estimated that there were 425 million diabetics (18–99 years old) worldwide, and this number could rise to 693 million by 2045.¹

The complications of diabetes, including atherosclerosis, diabetic kidney disease, diabetic retinopathy, and diabetic neuropathy, seriously affect patients' quality of life. Diabetic peripheral neuropathy (DPN) refers to the occurrence of symptoms and/or signs associated with peripheral nerve dysfunction in diabetic patients,

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excluding other causes (connective tissue disease, severe spondylosis, alcoholic neuropathy), including numbness, pain, abnormal movement, foot ulcers, gangrene, and even disability or death. These symptoms are characterized by peripheral nervous system involvement, which is the most common complication of diabetes.^{2,3} DPN is an insidious, variated pathology that is associated with foot ulceration, as well as morbidity and mortality and a significant reduction in quality of life.^{4,5}

Diabetic patients have been estimated to require surgery at least twice as often as non-diabetic patients, due to their comorbidities and the types of surgery performed.⁶ They are predestined to undergo many procedures under regional anesthesia.

Both electric nerve stimulation and ultrasound-guided localization of peripheral nerves are established techniques to conduct peripheral nerve blocks. The development of ultrasound imaging allows direct visualization of the structures of nerves, real-time needle guidance to the target nerve, and diffusion after local anesthetic injection, thereby improving the nerve positioning accuracy. Previous studies have shown the advantages of ultrasound imaging in patients.^{7,8} However, the sciatic nerve is located deep in the body, under the subgluteal nerve, lumbar plexus, and sacral plexus nerve, thus, the insertion angle of the needle can be very steep, impeding the visualization of the nerve and needle. It is necessary to perform nerve block under double guidance with stimulation and ultrasound in this situation. Electrical peripheral nerve stimulation (PNS) is a common technique for identifying the needle endpoint during the administration of nerve blocks.⁹ The current stimulation threshold of 0.3–0.5 mA has been established to deliver sufficient stimulation to induce a motor response while causing minimal discomfort to the patient.¹⁰ Generally, a current intensity of <0.3 mA indicates that the needle may cause nerve damage, and it recommended to reposition the needle to avoid peripheral nerve sheath injection.¹¹ However, some studies reported that in patients with increased risk of peripheral neuropathy, the motor response of the sciatic nerve to electrical stimulation has altered.^{12–14} Therefore, this study aimed to determine the effect of diabetes and DPN on the minimum stimulation which excites the corresponding muscle during sciatic nerve block.

Patients and Methods

Patients

Patient collection started in March 2019 and ended in October 2019. All patients underwent surgery in an

affiliated hospital of Guangxi Medical University. Sixty-five American Society of Anesthesiologists (ASA) I–III patients (>18 years old) who were scheduled for lower leg, foot, and ankle surgery due to ulcers, debridement, amputation, etc., received a sciatic and femoral nerve block. Five patients were not suitable for peripheral nerve block; three were excluded due to reoperation within 1 month, and two were excluded because they could not cooperate during the execution of the peripheral nerve block. Finally, a total of 60 patients were selected for observation. Patients did not undergo continuous anticoagulation treatment and did not have a local anesthetic allergy or a history of alcohol abuse. Among the 60 patients, 34 patients diagnosed with diabetes were divided into the diabetic patients group (group D, $n = 34$) and 26 people did not have diabetes (group ND, $n = 26$). Exclusion criteria included pregnancy, ongoing dual platelet therapy, allergies to local anesthetics, a history of alcohol abuse, ipsilateral sciatic nerve block within 1 month, and patients who could not cooperate during nerve block.

All included patients were screened preoperatively for signs of neuropathy by Dr. Chen Yifeng, who has received DPN screening training in endocrinology, based on the Toronto Clinical Scoring System (TCSS).

This trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Review Committee of the First Affiliated Hospital of Guangxi Medical University (Ethical Committee Number: 2019/KY-E-005) and started on March 1, 2019, and ended on October 31, 2019. It was registered with the China Clinical Trial Center (Registration Number: ChiCTR1900021495). Written informed consent was obtained from all subjects.

Diabetic Peripheral Neuropathy

All included patients were screened preoperatively for signs of neuropathy, based on the TCSS.¹⁵ Neurological symptoms included numbness, pain, acupuncture-like sensation, fatigue, walking instability, and corresponding symptoms of the upper limb (score 0 = asymptomatic, 1 = symptomatic). Nerve reflexes included knee and ankle reflexes, which were scored on both sides (score 0 = normal, 1 = weak, 2 = no reflex). Vibration perception was assessed using a 128-Hz tuning fork, and the position of patients' toes was checked by letting the patients judge the movement and the direction of movement, both rated as normal or abnormal (score 0 = normal, 1 = abnormal).

10 g perception of pressure by a 10 g monofilament, pain sensation by the pinprick test, and temperature discrimination by a device that tests the subject's ability to distinguish two materials of differing thermal conductivity (tip therm GmbH, Brueggen, Germany) were all scored as present or absent (score 0 = present, 1 = absent). The outcome was a clinical neuropathy score, ranging from a minimum of 0 to a maximum of 19 points. TCSS $\leq$ 5 was considered as no DPN, 6–8 was mild DPN, 9–11 was moderate DPN, and 12–19 as severe DPN.

Anesthesia Method

After the patient entered the operating room, vital signs were monitored which included three-lead electrocardiogram, automated non-invasive blood pressure, and pulse oximetry monitoring. All patients were intravenously infused with Ringer's lactate solution at a rate of 4–6 mL/(kg.h) and subjected to sciatic nerve and femoral nerve block under ultrasonic localization. In some patients, this was combined with general anesthesia. After cleaning the skin with an antiseptic solution, a SonoSite S-Nerve ultrasound machine (SonoSite, WA, USA) with a high-frequency linear array transducer was used to identify the sciatic nerve (Figure 1). A stimulating needle (22G, 80–100 mm, UniPlex Nanoline, Germany) was connected to the nerve stimulator (Stimuplex, HNS 11, B. Braun, Melsungen, Germany). Under real-time ultrasound guidance, using a short-axis in-plane technique was used to insert the stimulating needle into the sciatic nerve, until the nerve stimulation needle was in close contact with the nerve without penetration of the epineurium (Figure 2A). The needle tip location was confirmed by three signs on

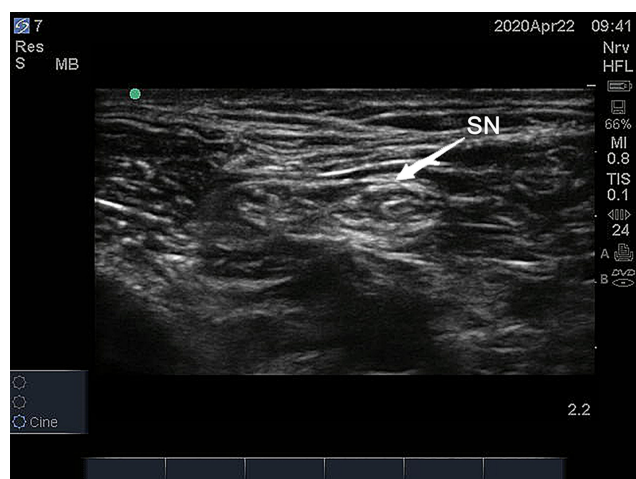


Figure 1 Sciatic nerve image under ultrasound scan. SN, sciatic nerve.

ultrasound: (1) the needle tip was localized next to the nerve, (2) when the needle was slightly advanced, the nerve was pushed away, and (3) when the needle moved forward and backward, the nerve did not follow the retreat of the stimulating needle, which indicated that the needle tip has not penetrated the epineurium. The nerve stimulator was set at a current intensity of 0.0 mA, a pulse width of 0.1 ms, and a stimulation frequency of 1 Hz. The stimulation current was gradually increased until a visible motor response of the respective muscles appeared (foot dorsiflexion, plantar flexion, foot valgus or adduction, and a toe bending response). Then, the current was decreased until the motor response vanished. The minimal stimulation threshold current was recorded (primary outcome). The anesthesiologist performing the nerve block was blinded to the stimulation current and did not move or reposition the needle tip during the measurement. Subsequently, 20 mL ropivacaine 0.5% was injected after negative aspiration (Figure 2B).

As for the femoral nerve block, patients were placed in a supine position and abducts the affected limb was abducted slightly. The ultrasound probe was placed horizontally in the groin, from outside to inside. The femoral nerve, artery, and vein could be visualized, and then 20 mL of 0.375% local was injected locally to wrap the femoral nerve. Sedation was achieved by continuous infusion of dexmedetomidine ($0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), and the infusion rate was adjusted according to blood pressure and heart rate during surgery. In patients with incomplete sensory or motor blocks, anesthesia was supplemented with analgesic drugs, such as low-dose fentanyl ($0.05 \mu\text{g}$, total $1.0 \mu\text{g}$) or 5 mg dezocine. Some patients completed surgery under a nerve block combined with general anesthesia, and we always started general anesthesia after completing the nerve block. General anesthesia was induced using propofol ($2.5\text{--}3.5 \mu\text{g/mL}$) and remifentanyl ($2.5\text{--}3.5 \text{ ng/mL}$) target-controlled infusion (TCI). The patients were intravenously injected with cisatracurium benzenesulfonate ($0.15\text{--}0.2 \text{ mg/kg}$) after falling asleep. Endotracheal intubation and mechanical ventilation were performed after the drug was effective. The anesthesia was maintained with propofol (TCI concentration, $1.0\text{--}2.5 \mu\text{g/mL}$), remifentanyl (TCI concentration, $1.0\text{--}3.0 \text{ ng/mL}$), and inhalation of 1–1.5% sevoflurane. Anesthetic administration was adjusted according to the patient's hemodynamics.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 (IBM Corporation, New York, USA). Normally distributed

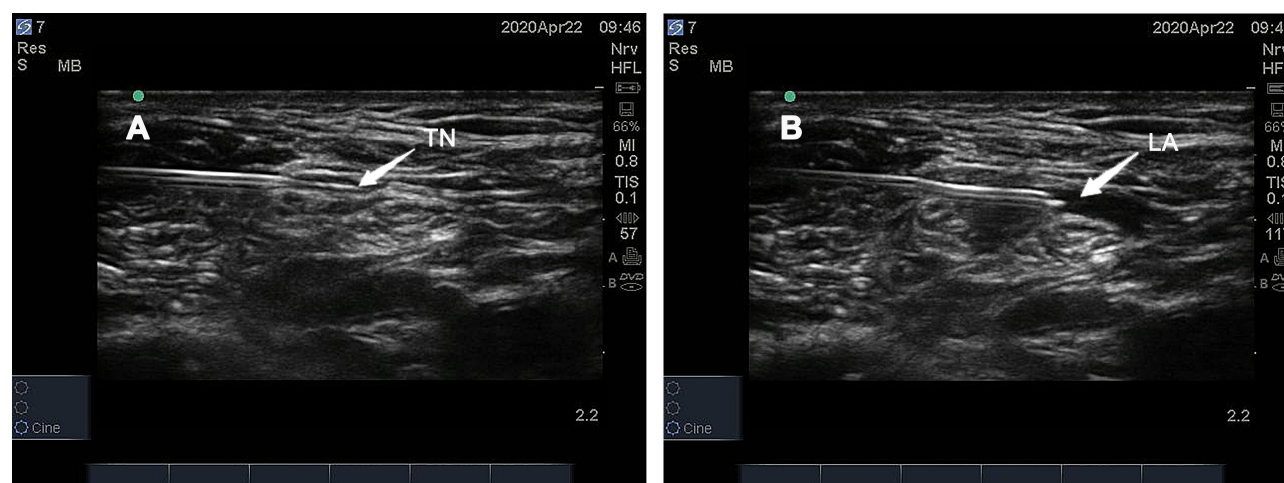


Figure 2 Needle tip position for measurement of the stimulation threshold (A) and local. Anesthetic (B).

Abbreviations: TN, Needle tip; LA, Local anesthetic.

continuous variables are expressed as the mean $\pm$ standard deviation (SD), and the analysis of differences between two groups was done using the independent-sample Student's *t*-test. Categorical variables are reported as proportions and analyzed by the Chi-square test. The frequency of categorical variables was analyzed using Fisher's exact test. Results were considered significant if $P < 0.05$.

Results

Baseline Characteristics of the Study Population

A total of 60 patients, including 34 diabetic (group D) and 26 non-diabetic patients (group ND), were included in the study.

In the diabetes group, 26 (76.5%) patients were diagnosed with DPN, and eight (23.5%) patients did not have DPN. Seven (26.9%), 11 (42.3%), and eight (30.8%) patients had mild, moderate, and severe DPN, respectively.

All the patients in the control group had no DPN. The demographic, clinical, and biological characteristics of patients are reported in Table 1. Diabetic patients had an older age and disease duration compared to the control group (age: 63.3 ± 10.6 vs 51.4 ± 14.0 , $P = 0.001$; duration: $P < 0.001$). There were also significant differences in ASA level, fasting blood glucose, and glycated hemoglobin ($P = 0.008$, $P < 0.001$, $P < 0.001$, respectively). In the diabetes group, patients had higher rates of coronary heart disease, uremia, and DPN ($P < 0.05$).

Electrical Stimulation Threshold

As shown in Figure 3A, there was a significant difference in the electrical stimulation threshold between the diabetes

group and the control group according to the independent-sample Student's *t*-test (1.0 ± 0.7 vs 0.4 ± 0.1 mA, $t = -5.088$, $P < 0.001$). There was also a significant difference in the stimulation current for the sciatic nerve between patients with and without DPN in the diabetes group (1.2 ± 0.7 vs 0.4 ± 0.1 mA, $t = -5.714$, $P < 0.001$, Figure 3B).

However, as illustrated in Figure 3C, the stimulation current did not differ between diabetic patients without DPN (0.4 ± 0.1) mA and non-diabetic patients (0.4 ± 0.1) mA. Additionally, stimulation currents of >3 mA were necessary to evoke a motor response in three patients who suffer from DPN.

We found that the TCSS score had a linear relationship with the electrical stimulation threshold (Figure 4) according to a simple linear regression model with a coefficient of determination (R^2) of is 49.3% ($F = 31.063$, $P < 0.001$) according to variance analysis. Thus, those findings implied that the equation was statistically significant ($P < 0.05$). Besides, $a = 0.008$ ($t = 0.041$, $P = 0.968 > 0.05$), $b = 0.125$ ($t = 5.573$, $P < 0.001$) in the regression equation, so electrical stimulation threshold (mA) = 0.125 TCSS score. Among them, three patients in whom we failed to elicit the corresponding muscle group response had TCSS scores of 12, 13, and 15.

Discussion

In the present study, we aimed to determine the effect of DPN on the current threshold for nerve stimulation during popliteal sciatic nerve block, to explore the relationship between the TCSS score and peripheral neuropathy. Our study revealed that participants with diabetes needed higher

Table I Demographic, Clinical, and Biological Characteristics in Patients with and without Diabetes

	Group ND (n=26)	Group D (n=34)	P
Age (years)	51.4±14.0	62.3±10.6	0.001
Gender (male/ female)	18/8 (69.2/ 30.8%)	24/10 (70.6/ 29.4%)	0.909
BMI (kg/m ²)	23.4±3.7	22.9±3.6	0.606
Diabetes duration[n (%)]			–
Non	26 (100.0)	0 (0.0)	
5 years	–	14 (41.2)	
≥ 5 years	–	20 (58.8)	
ASA[n(%)]			0.008
I	3 (11.5)	0 (0.0)	
II	22 (84.6)	24 (70.6)	
III	1 (3.8)	10 (29.4)	
Hypertension [n(%)]			0.111
Yes	5 (19.2)	13 (38.2)	
No	21 (80.8)	21 (61.8)	
CAD[n(%)]			< 0.001
Yes	0 (0.0)	29 (85.3)	
No	26 (100.0)	5 (14.7)	
Uremia[n(%)]			0.008
Yes	0 (0.0)	8 (23.5)	
No	26 (100.0)	26 (76.5)	
FBGe(mmol/L)	4.8±0.8	8.7±3.8	< 0.001
HbA1c(%)	5.6±0.6	8.8±2.7	< 0.001
DPN[n(%)]			< 0.001
Yes	0 (0.0)	26 (76.5)	
No	26 (100.0)	8 (23.5)	

Note: Data are presented as mean ± SD or %.

Abbreviations: BMI, body mass index; HbA1c, glycosylated hemoglobin; CAD, coronary atherosclerosis heart disease; FBG, fasting blood glucose albumin.

stimulation currents to evoke motor responses, and the electrical stimulation threshold (mA) = 0.125 TCSS score.

Diabetes Mellitus and Electrical Stimulation Threshold

There is a considerable prevalence of peripheral neuropathy in patients with diabetes mellitus.^{16,17} Our screening showed that a high prevalence of peripheral neuropathy was found in diabetic patients; 26 patients (76.5%) suffered from DPN. As is well known, motor

and sensory peripheral nerve function deteriorates with the occurrence of microangiopathy and may be associated with the development of peripheral neuropathy.¹⁸ We noted that diabetic patients require, on average, a higher stimulation threshold than control patients, which is in agreement with previous research. Keyl et al compared diabetic patients scheduled for surgical treatment of diabetic foot gangrene and non-diabetic patients undergoing orthopedic foot or ankle surgery.¹⁹ They observed that the geometric mean of the motor stimulation threshold of diabetic patients during popliteal nerve block was 1.9 (95% confidence interval [CI], 1.6–2.2), compared to 0.26 (95% CI, 0.24–0.28) of non-diabetic patients, indicating an increase by a factor of 7.2. Bigeleisen et al showed that the median stimulation threshold of diabetic patients undergoing supraclavicular brachial plexus blockade was 1.3 mA, while that of non-diabetic patients was 0.5 mA.²⁰ The threshold of electrical stimulation in diabetic patients was increased, which may be explained by mitochondrial oxidative dysfunction, oxidative stress, inflammation, decreases in Na⁺-K⁺-ATPase activity, loss of myelinated fibers, and demyelination. These factors lead to the slowdown of nerve conduction velocity, the decrease of action potential amplitude and the decrease of excitability, which are due to the insufficiency of peripheral blood vessel function, the changes of immunity and metabolism, as well as the change of sodium-calcium channel expression.^{21–23}

In addition, the present study demonstrated that the stimulation threshold of patients with diabetes and DPN was higher compared with patients without DPN. On the other hand, we observed no statistical difference in the stimulation threshold in diabetics without neuropathy and non-diabetic patients ((0.4 ± 0.1) mA vs (0.4 ± 0.1) mA), which was in accordance with the very small variation in stimulation thresholds in healthy volunteers.^{10,24} This suggests that peripheral neuropathy, rather than the diagnosis of diabetes mellitus, is the critical predictor of altered nerve responses to regional anaesthesia, increasing the average nerve stimulation threshold. Diabetic neuropathy is associated with a profound change in nerve physiology, resulting in changes in nerve excitability.^{25,26} However, in terms of diabetic patients without DPN, their nerve conduction velocity was not changed significantly, which explained that their stimulation threshold was the same as that of healthy patients.

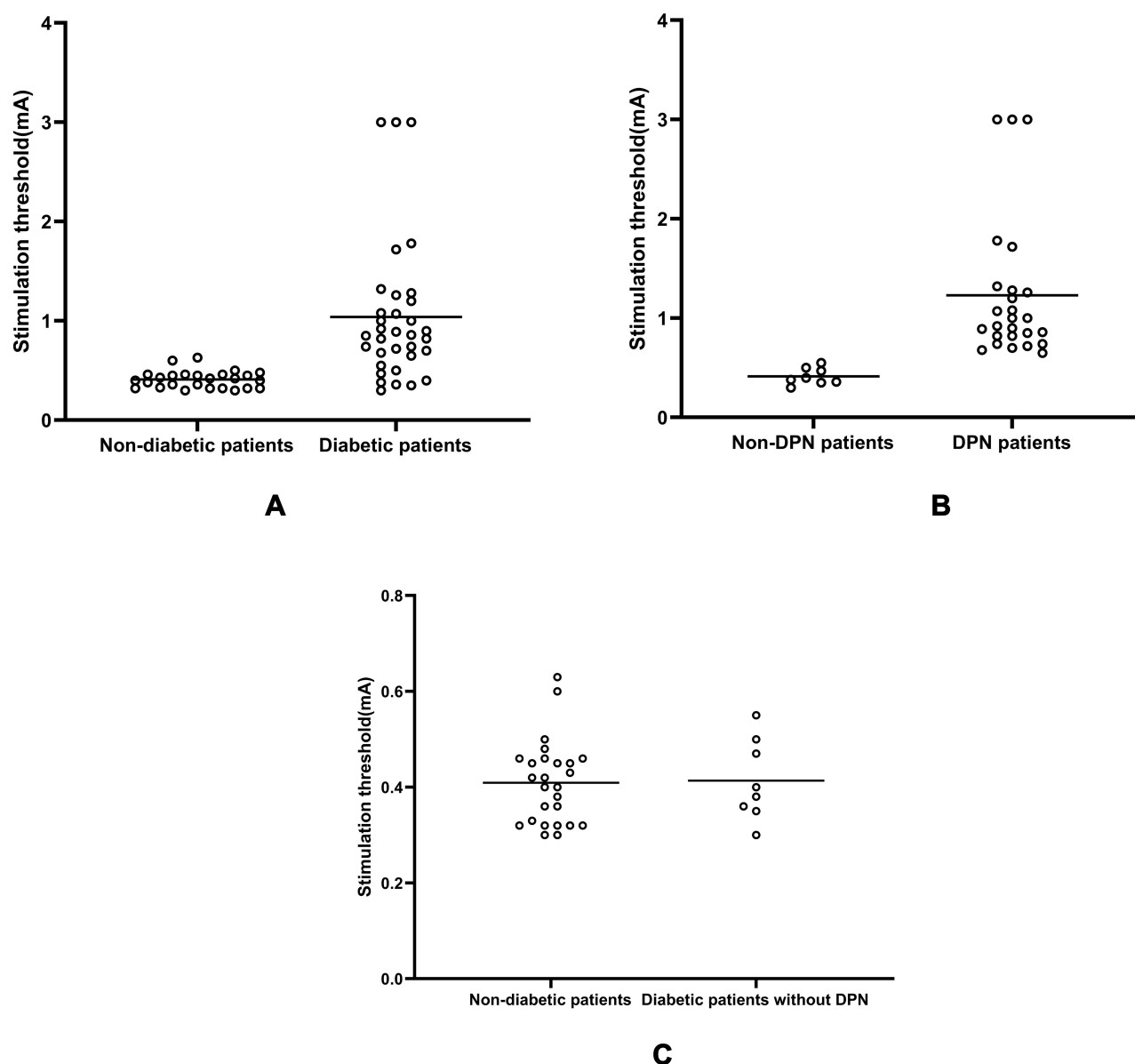


Figure 3 Comparison of electrical stimulation thresholds: (A) between non-diabetic and diabetic patients; (B) between DPN free group and DPN group; (C) between non-diabetic group and diabetic group without DPN. $P < 0.001$.

Correlation of DPN and Electrical Stimulation Threshold

DPN may increase the threshold of nerve electrical stimulation, but comprehensive studies of the relationship between the severity of DPN and the stimulation threshold are lacking. In our diabetic patients, we observed a linear correlation between the TCSS score and the stimulation threshold for the sciatic nerve: sciatic nerve electrical stimulation threshold (mA) = 0.125 TCSS. TCSS reflects the severity of peripheral neuropathy, which is positively correlated with DPN. Previous research has confirmed a significant

association between long duration of diabetes and DPN: the longer was the duration of diabetes, the more severe was peripheral neuropathy.^{27,28} Besides, a strongly positive association of diabetic neuropathy with HbA1c levels has been reported. Nisar et al found diabetics with HbA1c levels higher than 6.5% were 16.9 times more likely to develop neuropathy compared with controls.²⁹ The severity of hyperglycemia and abnormal hemoglobin levels have a great influence on the results of sensory and motor nerve conduction tests, which have an important influence on the stimulus threshold.³⁰ Heschl reported the minimum current threshold showed a highly significant negative correlation with

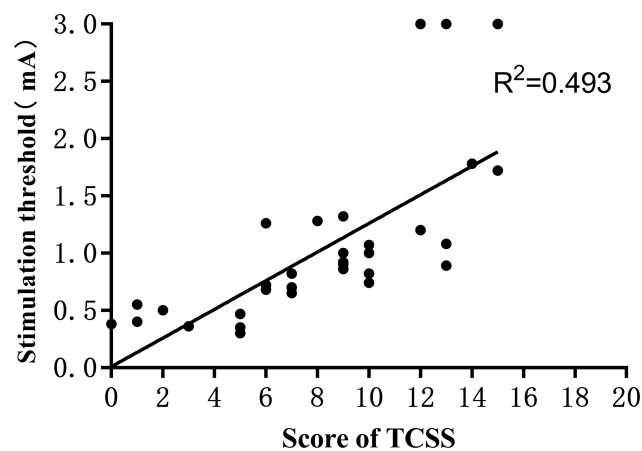


Figure 4 Linear relationship between TCSS score and electrical stimulation threshold.

a conduction velocity of the peroneal and ulnar nerves, and a positive correlation with the latent period of the action potential of the tibial and ulnar nerves.³¹ The correlation of the threshold with nerve conduction velocity was significant. With the aggravation of DPN, the conduction velocity and amplitude of motor nerves decreased significantly, resulting in an increase in the stimulation current required to elicit the corresponding motor response and thus a higher electrical stimulation threshold. Finally, we observed that three diabetic patients even required stimulation currents of >3 mA to evoke a motor response despite the needle being close to the nerve. We suggest that unsuccessful stimulation of movement in these three patients might be related to their severe neuropathy. If electrical peripheral nerve stimulation is used as the sole tool to identify correct needle position, these patients are at high risk for intraneural needle placement and subsequent nerve damage. The proportion of these patients in the diabetes group is significantly higher, and special caution should be taken when performing nerve block anesthesia without ultrasound assistance. It is recommended to use ultrasound and other tools to assist in positioning so as to improve the safety of these patients with regional anesthesia.

Limitations

First of all, the definition of our diabetic patient cohort was based on the clinical diagnosis. Patients with chronic kidney disease were selected for the present study, and in these patients the kidney disease caused by diabetes itself could not be clearly distinguished from that caused by other factors, which would develop into neuropathy.³²

Furthermore, DPN is associated with the occurrence and development of muscular atrophy, which might further alter the motor response to nerve stimulation.^{33,34} The main limitation of our study is that the sample size was small; in particular, the number of patients with different TCSS scores for DPN was limited.

Conclusions

This study demonstrated that the electrical stimulation threshold of diabetic patients was increased when compared to non-diabetic patients during popliteal sciatic nerve block, and the threshold of electrical stimulation of the sciatic nerve increases with the severity of diabetic nerve dysfunction.

Data Sharing Statement

The data supporting the discovery of Diabetic Peripheral Neuropathy Increases Electrical Stimulation Threshold of Sciatic Nerve: A Prospective parallel cohort Study have been stored in the ResMan Research Manager repository. We intend to share individual deidentified participant data, and all clinical data of collected patients. Besides, the statistical results and ethical approval consent are available. The time of sharing the original data within 6 months after the trial complete, and no expiry date. Anyone who wants to obtain data, can log in to <http://www.medresman.org.cn/login.aspx> to get it.

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Author Contributions

All authors contributed to data analysis and drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. All authors have agreed on the journal to which the article will be submitted.

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Disclosure

The authors report no conflicts of interest in this work.

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