Original paper

Folia Neuropathologica

Correlation analysis between plasma fibrinogen and nerve electrophysiological changes in type 2 diabetic peripheral neuropathy

Weili Gu[1,2*], Zhenhong Li[1,2*], Xiaobei Zhu[2], Xiaojuan Huang[2], Dengfeng Zhang[2], Yu Jiang[2], Zhaotian Ye[2], Ying Sun[2], Pian Ao[1], Xinyue Zhang[1], Qimin Cao[2], Li Wei[1], Shaojun Wang[3]

[1]College of Basic Medicine, Guangxi Medical University, Nanning, China, [2]Department of Ultrasound Diagnosis, 923 Hospital of the People's Liberation Army, Nanning, China, [3]Maternity and Child Health Care of Guang Xi Zhuang Autonomous Region, Nanning, China

*These authors contributed equally to this study.

Folia Neuropathol 2023; 61 (2): 153-162 *DOI: https://doi.org/10.5114/fn.2023.126609*

Abstract

Introduction: *The aim of the study was to investigate the pathogenesis of diabetic peripheral neuropathy (DPN) and the value of fibrinogen (FIB) in the early diagnosis of DPN.*

Material and methods: *A total of 121 patients with type 2 diabetes mellitus (T2DM) and DPN hospitalized in the Endocrinology Department of the 923 Hospital of the People's Liberation Army of China were randomly selected between May and October 2020 and divided into a T2DM asymptomatic (no peripheral neuropathy-related symptoms) group (66 cases) and a T2DM symptomatic group (55 cases) according to the presence or absence of clinical neurological symptoms and signs. Forty healthy volunteers were selected as a normal control group. In addition to plasma FIB and nerve electrophysiological tests, all included subjects were electrophysiologically tested for nerve conduction velocity (NCV), terminal motor latency (DML), sensory nerve action potential (SNAP) amplitude, and compound muscle action potential (CMAP) amplitude.*

Results: *Compared with the control group, NCV was slowed down in T2DM patients, DML was prolonged, and the amplitude of CMAP and SNAP were decreased. Compared with asymptomatic T2DM patients, symptomatic patients had slower NCV, longer DML, lower CMAP amplitude of median nerve, ulnar nerve and tibial nerve, and significantly lower SNAP amplitude of median nerve and ulnar nerve. CMAP amplitudes were decreased, and median and ulnar nerve SNAP amplitudes were also significantly decreased ($p < 0.05$). The plasma FIB concentration of asymptomatic patients with T2DM was higher than that of the control group, and the plasma FIB concentration of symptomatic patients with T2DM was higher than that of asymptomatic patients with T2DM ($p < 0.01$). The NCV and DML of asymptomatic patients with T2DM slowed down and prolonged as the FIB level increased; the NCV of T2DM symptomatic patients also slowed down as FIB increased, and median and ulnar nerve DML increased as FIB increased. There was no correlation between NCV and DML and the plasma FIB level in the control group. SNAP amplitudes of symptomatic and asymptomatic patients with T2DM decreased as plasma FIB increased, while CMAP amplitudes of the tibial nerve and the T2DM symptomatic ulnar nerve decreased as FIB increased in the control group.*

Conclusions: *FIB may be a contributing factor for diabetic neuropathy and could be used as an indicator in the early screening and diagnosis of peripheral neuropathy in patients with T2DM.*

Key words: *diabetes mellitus type 2, fibrinogen, diabetic peripheral neuropathy, nerve electrophysiology.*

Communicating author:

Li Wei, College of Basic Medicine, Guangxi Medical University, Nanning 530021, China, No. 22 of Shuangyong Road, Qingxiu District, Nanning 530021, China, phone: +86 07715358212, e-mail: weili_lsk@126.com; Shaojun Wang, Maternity and Child Health Care of Guang Xi Zhuang Autonomous Region, Nanning 530005, China, No. 225 Xinyang Road, Xixiangtang District, Nanning 530005, China, phone: +86 07713153941

Introduction

Diabetic peripheral neuropathy (DPN) refers to the presence of symptoms and signs related to sensory, motor, and autonomic dysfunction in patients with diabetes that exclude other factors [23]. DPN is the most common complication of diabetes [16]. Type 2 diabetes mellitus (T2DM) accounts for more than 90% of diabetic patients. The incidence of T2DM neuropathy has been reported as 59%. Once it has arisen, DPN is irreversible. It eventually leads to limb gangrene and even amputation, affecting the quality of life of patients with diabetes [16]. However, the occurrence, development, prognosis, prevention, and treatment of DPN are not yet fully understood. However, nerve conduction studies are labour intensive, time consuming, and costly; therefore, implementing them in routine clinical care is impractical [18]. Beyond improving blood sugar control, no licensed pathognetic treatment for diabetic neuropathy is currently available [8]. Researchers such as Coban [3] have found that diabetes can increase the level of fibrinogen (FIB) in the body, which is closely related to neurodegenerative changes.

Fibrinogen, which is also known as coagulation factor I, is a macromolecular glycoprotein synthesized by the liver and the most abundant coagulation factor in the blood. Coagulation, platelet aggregation, and vascular endothelial cell function affect the blood vessels [1]. Research on FIB has long focused on the role of physiological haemostasis in the body. Recent studies have shown that FIB can be deposited in nerve tissue through damaged blood vessels or the blood-nerve barrier and cause neurological dysfunction. However, few studies have been conducted on the role of plasma FIB in peripheral neuropathy in patients with T2DM. Further, there is a lack of simple markers for the early detection of DPN in routine clinical practice [18].

This study used electrophysiological testing to evaluate the neurological function of patients with T2DM and analysed the correlation between the electrophysiological changes of the peripheral nerves and the level of plasma FIB in patients with T2DM. The results of this study provide a basis for the early screening and diagnosis of neuropathy in patients with T2DM and a new way of exploring the mechanisms of DPN.

Material and methods

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the 923rd Hospital of the People's Liberation Army.

This was a retrospective study. Data on 121 patients with T2DM admitted to the Endocrinology Department of our hospital between May and October 2020 were collected; the patients comprised 79 male subjects and 42 female subjects aged 23-86 years old, with an average of 51.56 ±10.42 years. The disease duration was from three months to 34 years, with an average of 7.45 ±6.21 years. Patients with T2DM were divided into a T2DM asymptomatic group (66 cases) and a T2DM symptomatic group (55 cases) according to the presence or absence of clinical symptoms and signs.

Inclusion criteria

The 2020 edition of the Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes were used as the diagnostic criteria for type 2 diabetes: (1) random blood glucose ≥ 11.1 mmol/l; (2) fasting blood glucose (GLU) ≥ 7.0 mmol/l; (3) oral glucose tolerance test (OGTT) test, two hours later, two-hour postprandial blood glucose (2 h PBG) ≥ 11.1 mmol/l; (4) Glycated haemoglobin ≥ 6.5%. Clinical neuropathy symptoms plus insulin resistance plus one of the above four conditions.

Exclusion criteria

The exclusion criteria were as follows: (1) a history of peripheral nerve trauma or nerve root irritation symptoms; (2) cervical spondylosis/lumbar disc herniation; (3) a long-term or heavy drinking history (i.e., an average intake of alcohol of over 250 g for over 10 years, mostly consumed on an empty stomach [2]), a history of occupational exposure to neurotoxins; (4) thyroid disease and the use of non-narcotic analgesics for pain relief; (5) bladder function lesions and liver and kidney function lesions caused by organic lesions [9]; (6) factors affecting nerve conduction velocity (NCV; e.g., mechanical pressure, freezing, muscle atrophy, chemical drugs); (7) cardiovascular and cerebrovascular diseases (e.g., stroke, myocardial infarction, atherosclerosis); and (8) related diseases associated with elevated plasma FIB (e.g., tumours, multiple sclerosis, chronic obstructive pulmonary disease, oedema).

Control group

Forty healthy individuals (n = 40) with no blood sugar and peripheral nerve abnormalities were selected during the same period. Of this number, 24 subjects were male, and 16 were female. The average age was 50.83 ±9.12 years. The study was approved by the Ethics Committee of our hospital.

Research methods

The medical history of patients with diabetes (including age, medical history, symptoms) and clinical parameters (e.g., FIB, 2 h PBG, HbA_{1c}) were collected.

Electrophysiological detection

The NCV of the limbs (median, ulnar, common peroneal, tibial, and superficial peroneal nerve) was measured using the American Nicolet VikingQuest EMG. Motor nerve conduction velocity (MCV), sensory nerve conduction velocity (SCV), compound muscle action potential (CMAP) amplitude, sensory nerve action potential (SNAP) amplitude, and distal motor latency (DML) were recorded. Indoor light was suitable, and the room was quiet during the detection process. The indoor temperature was controlled at approximately 25°C, and the subjects' limb temperature was maintained above 30°C.

Statistical analysis

GraphPad Prism 6.0 statistical software was used for the statistical analysis. The distribution of measurement data was expressed as mean ± standard deviation (±SD). The measurement data of the three groups were compared using a one-way ANOVA and the least significant difference test. The correlation between risk factors and neuropathy was analysed by linear regression and Pearson linear correlation analysis, and the significance level was defined as $p < 0.05$.

Results

Between May and October 2020, 121 patients were identified and enrolled in the study and divided into two groups. There were 42 male patients and 24 female patients in the T2DM asymptomatic group and 37 male patients and 18 female patients in the T2DM symptomatic group. The average ages of patients in the T2DM asymptomatic and T2DM asymptomatic groups were 51.15 ±11.64 and 55.21 ±10.76, respectively. There was no statistically significant difference between the two groups regarding gender or age ($p > 0.05$).

Neurophysiological changes in T2DM

Electrophysiological changes of motor nerves

Changes in the MCV, DML, and CMAP amplitudes of the upper and lower extremity motor nerves in the control group, asymptomatic T2DM group, and T2DM symptomatic group are shown in Table I. Median, ulnar, common peroneal, and tibial nerve MCV velocities were slowed, DML was prolonged, and the CMAP amplitude was decreased in patients with T2DM compared with the control group ($p < 0.01$). The MCV was slowed, and DML was prolonged in symptomatic patients with T2DM compared with asymptomatic patients. There was no significant difference in the CMAP amplitude of the common peroneal nerve between symptomatic and asymptomatic patients ($p > 0.05$), while the CMAP amplitudes of the median, ulnar, and tibial nerve in symptomatic patients with T2DM were significantly lower than those of asymptomatic patients ($p < 0.05$).

Electrophysiological changes of sensory nerves

Changes in the SCV and SNAP amplitudes of limbs in the control group, asymptomatic T2DM group, and T2DM symptomatic group are shown in Table II. Median, ulnar, and superficial peroneal nerve SCV were significantly slowed in patients with T2DM compared with the control group ($p < 0.05$), and the SNAP amplitude was significantly reduced ($p < 0.01$). In patients with T2DM, the SNAP amplitude of the superficial peroneal nerve showed no difference between symp-

Table I. Motor nerve conduction velocity (MCV), distal motor latency (DML) and compound muscle action potential (CMAP) amplitude comparison of three groups

Group	Cases	Median nerve	Ulnar nerve	Phil shallow nerve	Tibial nerve
MCV					
Control	40	51.81 ±1.93	53.55 ±2.01	47.24 ±1.09	43.07 ±1.56
T2DM asymptomatic	66	48.61 ±4.03**	49.87 ±3.76**	40.94 ±4.07**	38.89 ±3.01**
T2DM symptomatic	55	45.28 ±4.26#	45.83 ±4.99##	36.67 ±5.05##	36.08 ±4.48##
DML					
Control	40	3.14 ±0.43	2.49 ±0.28	3.44 ±0.42	3.08 ±0.61
T2DM asymptomatic	66	3.68 ±0.59**	2.94 ±0.34*	3.73 ±0.54*	3.74 ±0.43*
T2DM symptomatic	55	3.98 ±0.70#	3.27 ±0.52#	4.05 ±0.61#	4.10 ±0.60#
CMAP					
Control	40	13.55 ±1.03	12.27 ±1.81	6.71 ±1.01	15.80 ±1.20
T2DM asymptomatic	66	11.72 ±2.15**	11.05 ±1.32*	4.82 ±0.65	11.51 ±1.19
T2DM symptomatic	55	10.86 ±2.12 #	9.91 ±1.64#	4.62 ±0.98#	10.75 ±1.96#

*Compared with the control group,*p < 0.05, **p < 0.01; Compared with the T2DM asymptomatic group, #p < 0.05, ##p < 0.01*

Table II. Comparison of sensory nerve conduction velocity (SCV) and sensory nerve action potential (SNAP) among three groups

Group	Cases	SCV ($\bar{x}$ ±s, mV)			SNAP ($\bar{x}$ ±s, mV)		
		Median nerve	Ulnar nerve	Phil shallow nerve	Median nerve	Ulnar nerve	Phil shallow nerve
Control	40	53.12 ±1.15	56.24 ±2.04	55.42 ±0.88	18.14 ±2.28	12.17 ±2.75	10.44 ±2.81
T2DM asymptomatic	66	48.01 ±5.02*	47.91 ±4.72**	42.32 ±4.42**	10.91 ±1.87**	9.13 ±2.03**	8.20 ±2.24 **
T2DM symptomatic	55	43.29 ±7.35##	42.97 ±7.14##	37.59 ±5.16##	2.57 ±0.58##	1.57 ±0.30##	1.48 ±0.33##

*Compared with the control group,*p < 0.05, **p < 0.01; Compared with the T2DM asymptomatic group, #p < 0.05, ##p < 0.01*

Table III. Plasma fibrinogen (FIB) changes for control, T2DM asymptomatic and type 2 diabetes mellitus (T2DM) symptomatic groups

Project	Control (n = 40)	T2DM asymptomatic (n = 66)	T2DM symptomatic (n = 55)
FIB (mmol/l)	2.45 ±0.73	3.12 ±1.04 #	3.84 ±1.65*

*Compared with the control group, #p < 0.01; Compared with the T2DM asymptomatic group, *p < 0.01*

tomatic T2DM and asymptomatic patients with T2DM ($p > 0.05$), while the median nerve and ulnar nerve SNAP amplitudes of symptomatic patients with T2DM were significantly lower than those of asymptomatic patients with T2DM ($p < 0.05$).

Correlation analysis of plasma FIB level and NCV in patients with T2DM

Changes in plasma FIB levels in patients with T2DM

The maximum plasma FIB concentration in the control group was 4.44 g/l, the minimum was 1.5 g/l, and the average was 2.45 ±0.73 g/l, which was significantly lower than that of the T2DM group ($p < 0.01$). Among patients with T2DM, the maximum concentration of FIB in asymptomatic patients with T2DM was 6.89 g/l, the minimum concentration was 1.70 g/l, and the average was 3.12 ±1.04 g/l, while the maximum concentration T2DM symptomatic patients was 9.81 g/l, the minimum concentration was 1.13 g/l, and the average was 3.84 ±1.65, which was significantly higher than that of the asymptomatic T2DM group ($p < 0.01$; Table III).

Correlation analysis between plasma FIB changes and upper and lower extremity exercise NCV in patients with T2DM

The correlation analysis of plasma FIB with MCV and SCV in the control group, T2DM asymptomatic group, and T2DM symptomatic group is shown in Figures 1 and 2. The motor and sensory NCV of patients with T2DM slowed down as the blood FIB level increased, while the sensory and motor NCV of limbs in the control group was not correlated with changes in plasma FIB concentration.

Correlation analysis between plasma FIB changes and DML of the upper and lower extremities in patients with T2DM

The correlation between plasma FIB and DML in the control group, T2DM asymptomatic group, and T2DM symptomatic group is shown in Figure 3. The DML of the median and ulnar nerves in the upper extremities of patients with T2DM and the DML of the common peroneal and tibial nerves of the lower extremities in asymptomatic patients with T2DM were prolonged as the FIB concentration increased. The lower extremity common peroneal nerve DML and tibial nerve DML in symptomatic patients with T2DM were longer than those of the control group and patients with T2DM. The plasma FIB concentration was also higher than in symptomatic patients with T2DM compared with the control group and in patients with T2DM ($p < 0.05$), but there was no correlation between DML and FIB ($p > 0.05$). There was no correlation between the DML of the median, ulnar, common peroneal, and tibial nerve and the plasma FIB concentration in the control group ($p > 0.05$).

Correlation analysis between plasma FIB concentration and upper and lower extremity nerve CMAP amplitude and SNAP amplitude in patients with T2DM

The correlation analysis results of the control group, T2DM asymptomatic group, and T2DM symptomatic group for the limb nerve CMAP amplitude, SNAP

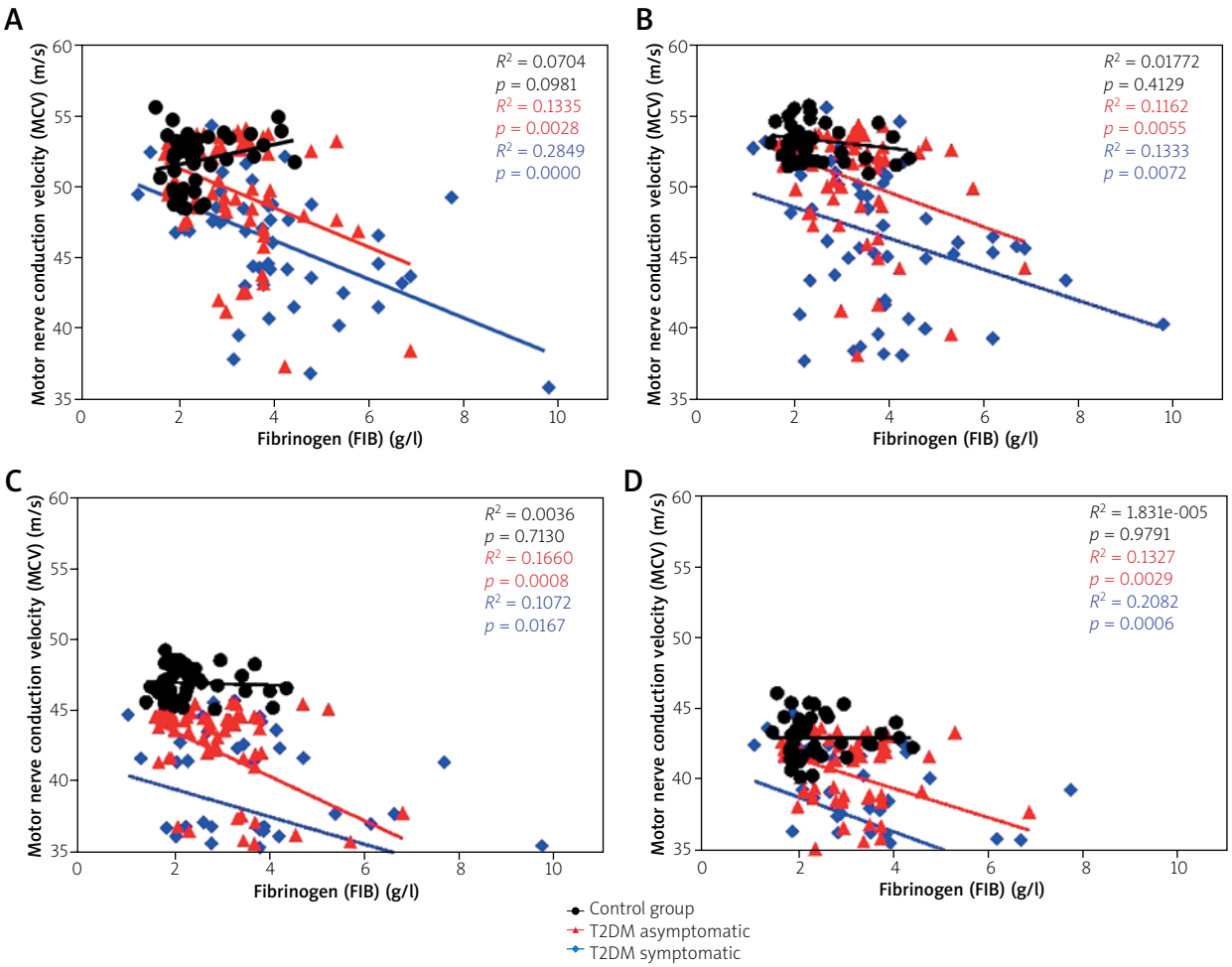

Fig. 1. Correlation analysis between fibrinogen (FIB) level and motor nerve conduction velocity (MCV) of **A**) median nerve, **B**) ulnar nerve, **C**) common peroneal nerve and **D**) tibial nerve for control, type 2 diabetes mellitus (T2DM) asymptomatic and T2DM symptomatic groups.

amplitude, and plasma FIB concentration are shown in Figures 4 and 5. The SNAP amplitude of limb nerves in patients with T2DM decreased as the plasma FIB concentration increased, while the CNAP amplitude decreased as FIB increased only in the tibial nerve in the control group and the ulnar nerve in the symptomatic T2DM group. No significant correlation was found in other nerves.

Discussion

At present, the main methods for diagnosing DPN are clinical symptoms and signs, pathological examination, and nerve electrophysiological testing [23]. Nerve electrophysiological testing is considered the gold standard for diagnosing DNP and is widely used in clinical practice due to its non-invasiveness [15]. In the present study, nerve electrophysiology was used to detect peripheral neuropathy in patients with T2DM. The results showed that the NCV of symptomatic patients with T2DM was slower than that of asymptomatic patients, the DML was prolonged, and the SNAP and CMAP amplitudes were lower, which is consistent with the clinical symptoms and signs of T2DM, as well as the findings of several other studies [12,14,24]. Further investigation found that the NCV of asymptomatic patients with T2DM was slower than that of the control group, the DML was prolonged, and the amplitudes of CMAP and SNAP were lower than those of the control group. This suggests that neurophysiological testing can not only determine the type and degree of nerve damage but also detect subclinical damage in asymptomatic patients with T2DM.

Fibrinogen, an acute-phase protein that is the first coagulation factor to reach extremely low concentrations on activation of coagulation and bleeding, is an indepen-

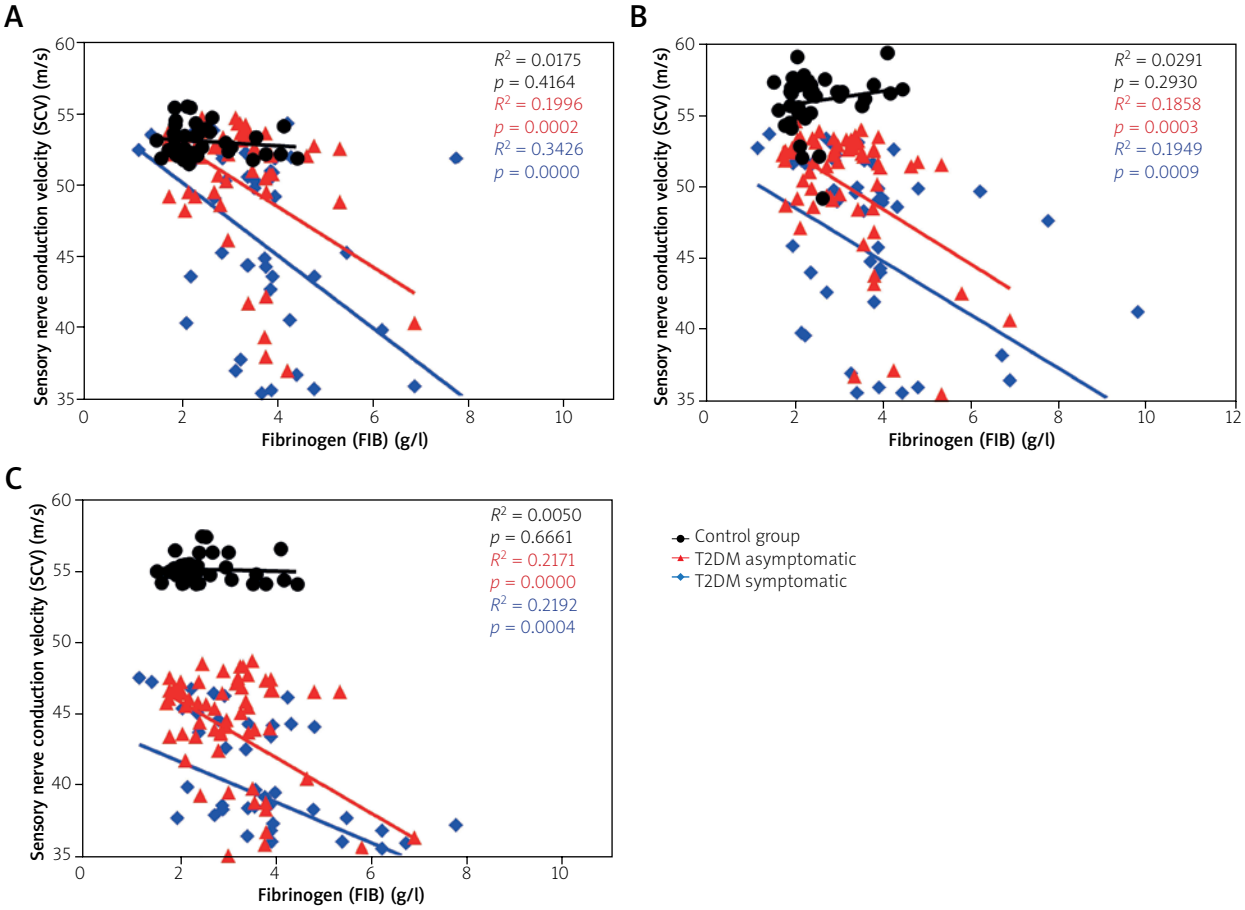

Fig. 2. Correlation analysis between fibrinogen (FIB) level and sensory nerve conduction velocity (SCV) of **A**) median nerve, **B**) ulnar nerve and **C**) superficial peroneal nerve for control, type 2 diabetes mellitus (T2DM) asymptomatic and T2DM symptomatic groups.

dent factor predicting death [7]. Research has found that FIB significantly influences infection, inflammation, and tissue repair. Metabolic changes in diabetes impair neurovascular supply and lead to changes in the neurophysiological function [22]. In the present study, disordered FIB metabolism was a key feature of patients with T2DM. Nerve damage in patients with T2DM increased as the FIB level increased, suggesting that patients with T2DM are in a more severe hypercoagulable state. It is thought that patients with T2DM are in a hyperosmolar state caused by high blood sugar and a prolonged high FIB concentration, which results in blood concentration, increased blood viscosity, and slowed fluidity, increasing the risk of blood coagulation, microvascular ischemia, and hypoxia [6]. In addition, elevated FIB levels lead to pathological changes, such as platelet aggregation, increased coagulation function, decreased fibrinolytic function, increased vascular permeability, and the destruction of vascular endothelial cell function, which promote the development of microvascular lesions and worsen ischemia and hypoxia status in neural tissue [11]. Recent research has also shown that soluble FIB in the blood can penetrate the nerve tissue through damaged blood vessels or the blood-nerve barrier, where it is converted into insoluble fibrin, promoting neurodegeneration and inhibiting remyelination. This finding sheds light on the occurrence, development, prognosis, and prevention of neuropathy [20]. The present study detected plasma FIB levels in patients with T2DM and healthy controls and found that levels in patients with T2DM were significantly higher than those of controls, consistent with clinical reports [13]. Although the causal relationship between elevated plasma FIB in patients with T2DM and the pathogenesis of T2DM is not yet clear, the present study found that plasma FIB levels in symptomatic patients with T2DM were higher than those of asymptomatic patients with T2DM, suggesting that FIB may be related to the occurrence, development, and outcomes of DPN. NCV and DML mainly reflect the function of myelin [10]. A reduction in MCV and SCV and a prolongation of DML are typical signs of DPN. This study found that NCV in symptomatic patients with T2DM was

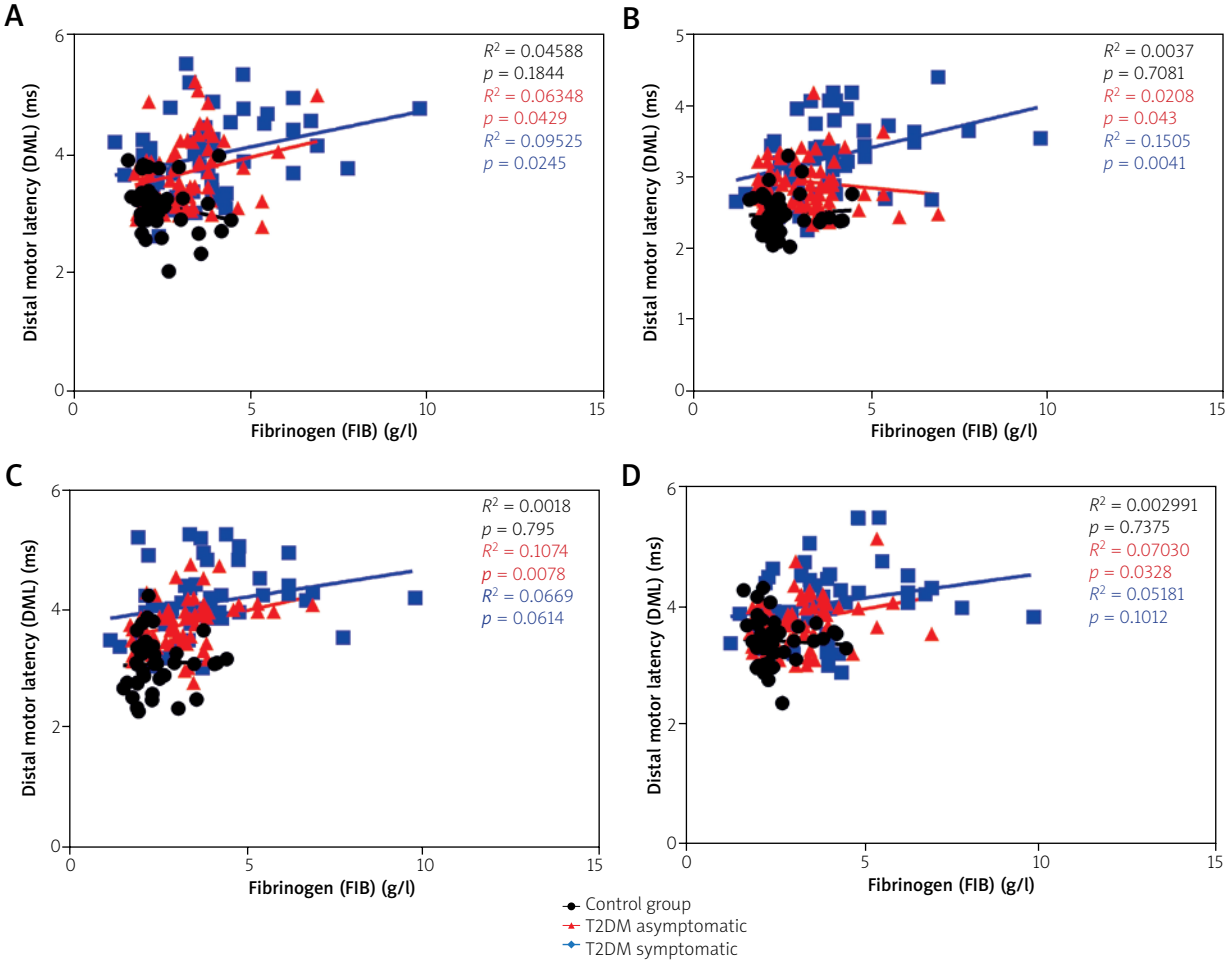

Fig. 3. Correlation analysis between fibrinogen (FIB) level and distal motor latency (DML) for **A**) the median nerve, **B**) ulnar nerve, **C**) common peroneal nerve and **D**) tibial nerve of control, type 2 diabetes mellitus (T2DM) asymptomatic and T2DM symptomatic groups.

significantly lower than that of asymptomatic patients, and DML was also prolonged compared with asymptomatic patients, which is consistent with clinical symptoms and signs. Further analysis showed that NCV in symptomatic patients with T2DM decreased as the plasma FIB concentration increased, and DML was prolonged as FIB increased, suggesting that FIB may promote the occurrence of peripheral nerve demyelination in symptomatic patients with T2DM. Analysis of the plasma FIB concentration, NCV, and DML in asymptomatic patients with T2DM also showed that patients' NCV decreased as the plasma FIB concentration increased, and DML was prolonged as FIB levels increased, further indicating that FIB affects myelin function in T2DM. Based on these findings, FIB could be used as an early screening and diagnostic index for myelin lesions in asymptomatic patients with T2DM. Compared with the asymptomatic T2DM group, the DML of the common peroneal nerve and the tibial nerve in symptomatic patients with T2DM was prolonged, and FIB was also higher than that of the asymptomatic T2DM group. The lack of correlation between DML and FIB requires further investigation, though a ceiling effect has been proposed as a potential explanation. The amplitudes of CMAP and SNAP mainly reflect axonal function [21]. In this study, the amplitudes of neural CMAP and SNAP in symptomatic patients with T2DM were significantly lower than those of asymptomatic patients, which is consistent with clinical symptoms and signs. The correlation analysis between the SNAP amplitude and FIB concentration in patients with T2DM showed that the SNAP amplitude in symptomatic patients with T2DM decreased as the FIB concentration increased, suggesting FIB may be related to the occurrence of T2DM nerve axonal injury and ulnar nerve CMAP amplitude in symptomatic patients with T2DM. The increase and decrease in FIB further confirm FIB's influence on axonal nerve function. The present study's correlation analysis between the SNAP amplitude and

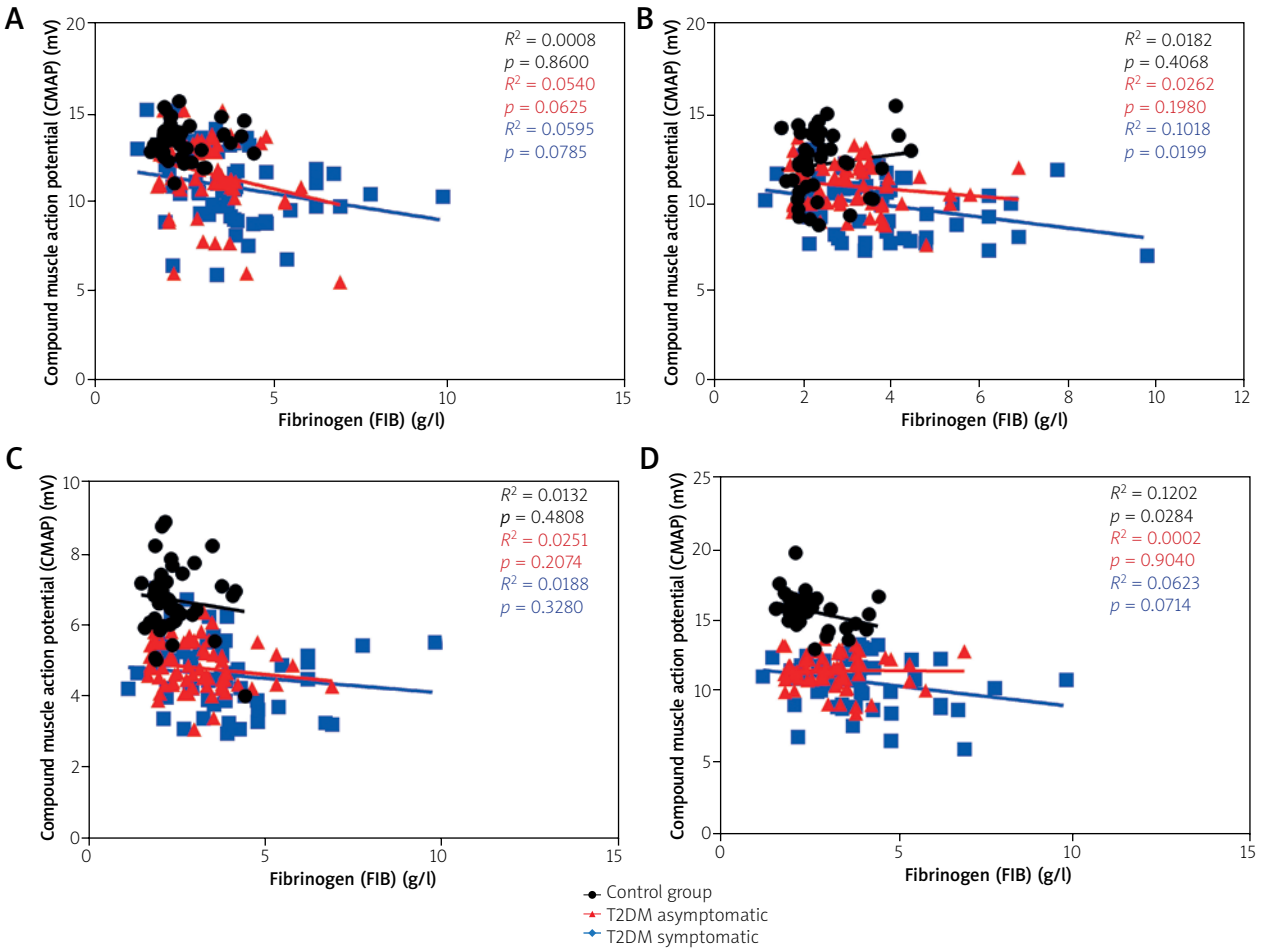

Fig. 4. Regression analysis of fibrinogen (FIB) levels and compound muscle action potential (CMAP) of **A**)the median nerve, **B**) ulnar nerve and **C**) superficial peroneal nerve for control, type 2 diabetes mellitus (T2DM) asymptomatic and T2DM symptomatic groups.

FIB concentration in asymptomatic patients with T2DM suggests that FIB could be used as an early screening and diagnostic index for peripheral nerve axonal injury in T2DM. The correlation between the CMAP amplitude and FIB in the control group further suggests that FIB also functions as an axon. T2DM neuropathy is associated with increased biochemical markers of inflammation and endothelial dysfunction, which are further increased in symptomatic patients [5]. Fibrinogen regulates coagulation and is also a pleiotropic blood protein for inflammation and tissue repair [25]. Further, in the nervous system, FIB is deposited before demyelination occurs, suggesting that FIB activates inflammatory demyelination [17]. The contraction of endothelial cells at the site of inflammation results in the deposition of exudated FIB in the form of FIB polymers outside the blood vessels. The translocation of FIB stimulates macrophages to secrete macrophage inflammatory protein (MIP)-1α, MIP-1β, MIP-2, macrophage chemoattractant protein (MCP)-1, and chemotaxis factor. These factors act on the T cells, neutrophils, and macrophages, inducing the accumulation of these cells at the site of inflammation [19] and increasing the infiltration of inflammatory cells into the tissue [4].

Our study has some limitations. First, we did not assess changes in plasma FIB during treatment. Second, the number of study subjects was relatively small. Third, this study was conducted in only one public hospital, which may not be representative of the entire Chinese population with DPN.

Conclusions

The present study found that FIB levels were significantly elevated in patients with DPN, and the degree of elevation correlated with the degree of neuropathy. Further experiments should be conducted to confirm

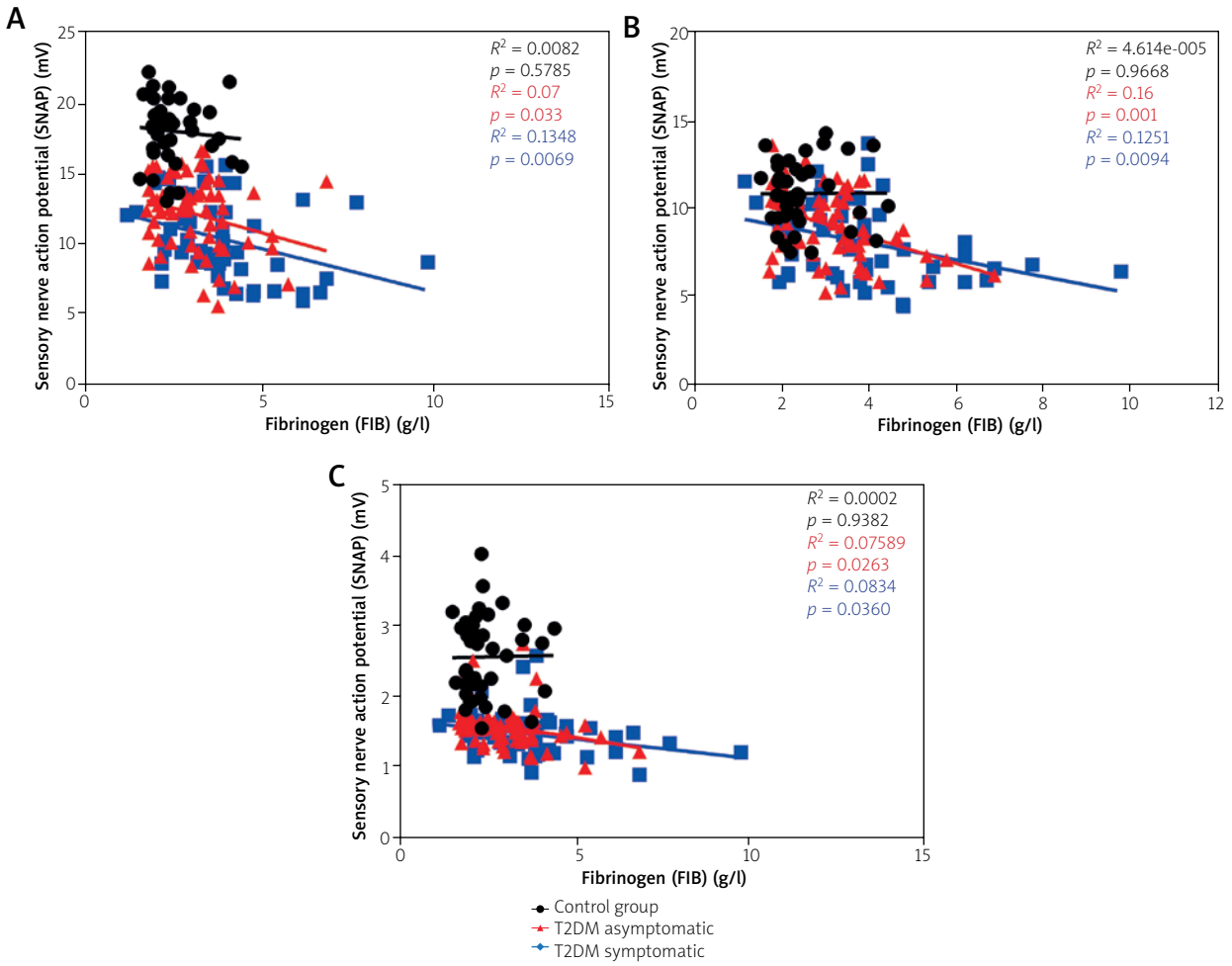

Fig. 5. Regression analysis of fibrinogen (FIB) levels and sensory nerve action potential (SNAP) of **A**) the median nerve, **B**) ulnar nerve and **C**) superficial peroneal nerve for control, type 2 diabetes mellitus (T2DM) asymptomatic and T2DM symptomatic groups.

this finding. We showed that FIB plays an important role in the occurrence, development, and prognosis of T2DM neuropathy. Although the mechanism of action of T2DM neuropathy is not yet clear, we believe that FIB can be used as an early screening and diagnostic indicator for T2DM neuropathy.

Funding

National Natural Science Foundation of China (81460479); Guangxi Natural Science Foundation Project (2018JJA140600). Guangxi Zhuang Autonomous Region Health Committee self-funded scientific research projects (Z-A20221025), (Z-A20221029).

Disclosure

The authors report no conflict of interest.

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