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Research article

Analysis of the effect of probucol-mecobalamin tablets combination on oxidative stress in patients with diabetic peripheral neuropathy

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ABSTRACT

Objective: This research aimed to observe the effect of probucol combined with mecobalamin tablets on oxidative stress in patients with diabetic peripheral neuropathy (DPN).

Methods: In this prospective study, 104 patients with DPN who were treated in our hospital were included, from August 2018 to January 2020. They were divided into groups of combination (n = 52) and control (n = 52) by using a random number table. All patients took mecobalamin tablets after meals for 3 months (1 tablet/time, 3 times/d). On this basis, patients in the combination group took probucol for 3 months (4 tablets/time, 2 times/d). The observation indicators were the Toronto Clinical Scoring System (TCSS)(symptom, sensory, and reflex scores), nerve conduction velocity[sensory nerve conduction velocity (SNCV) and motor nerve conduction velocity(MNCV) of the common peroneal nerve and median nerve], oxidative stress indicators[superoxide dismutase(SOD), malondialdehyde(MDA), glutathione peroxidase(GSH-Px) and catalase(CAT)], clinical efficacy and adverse reactions.

Results: There was no significant difference in the symptom scores, sensory scores, reflex scores, and total scores between the two groups before treatment ($p > 0.05$), while these four indicators of the combination group were significantly lower than that in the control group after treatment ($p < 0.05$). These four indicators of the two groups after treatment were significantly lower than before treatment ($p < 0.05$). There was no significant difference in the SNCV and NMCV of the common peroneal nerve and median nerve between the two groups before treatment ($p > 0.05$), while the indicators of the combination group were significantly higher than that of the control group ($p < 0.05$) after treatment, and these indicators of the two groups after treatment were significantly higher than that before treatment ($p < 0.05$). There was no significant difference in SOD, MDA, GSH-Px, and CAT between the two groups before treatment ($p > 0.05$). After treatment, the SOD, GSH-Px, and CAT in the combination group were significantly higher than that in the control group ($p < 0.05$), while the MDA in the combination group was significantly lower than that in the control group ($p < 0.05$). After treatment, the SOD, GSH-Px, and CAT in the two groups were significantly higher than that before treatment ($p < 0.05$), while the MDA was lower ($p < 0.05$). The clinical efficacy of the combination group was significantly better than that of the control group (94.23 % vs 78.85 %, $p < 0.05$) after treatment. There was no significant difference in the incidence of total adverse reactions between the two groups (3.85 % vs 5.77 %, $p > 0.05$).

Conclusion: The therapeutic effect of probucol combined with mecobalamin tablets for patients with DPN was significant, which could effectively improve the oxidative stress response of patients and was worthy of clinical promotion.

1. Introduction

Diabetic peripheral neuropathy (DPN) is a common and complex clinically chronic disease. The incidence of DPN in diabetic patients is about 60 %, and the incidence is rising in recent years. DPN can affect the autonomic, motor, and sensory nerves, then cause numbness, pain, autonomic dysfunction, and dyskinesia in the patients' limbs, and even cause amputation, which poses a serious threat to the patients' life and

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health [1,2].

At present, the pathogenesis of DPN is still unclear. Most researchers believe that DPN is caused by a combination of multiple factors such as insulin resistance, oxidative stress, metabolic inflammation, autoimmunity, disorders of glucose and lipid metabolism, and diabetic microangiopathy [3,4]. Recently, many studies reported [5,6] that the occurrence of DPN was related to neurotrophic disorders and metabolic factors, which were caused by endoneurium microvascular endothelial cell disease.

Unfortunately, there are no specific drugs for the treatment of DPN. The common treatment strategy is to repair nerves by nourishing nerves, improving peripheral microcirculation, and resisting oxidative stress. Among them, the most widely used strategy is antioxidant stress. Probucol can regulate lipid metabolism, besides, the United States Drug Administration (FDA) has approved this drug's effect against oxidative stress [7]. Mecobalamin tablets are derivatives of vitamin B12. Mecobalamin tablets can quickly enter nerve cells and participate in the protein, fat, and nucleic acid metabolisms. Thus, Mecobalamin tablets can stimulate the regeneration of nerve cell axons and accelerate the repair of damaged nerve tissue [8].

Presently, there are few reports on the efficacy of probucol combined with mecobalamin tablets on the treatment of patients with DPN. In this article, we will discuss the efficacy of the combined application of these two drugs, and provide a basis for the clinical treatment of patients with DPN.

2. Materials and methods

2.1. Research design

In this prospective study, 104 patients with DPN who were treated in our hospital were included, from August 2018 to January 2020. The patients were divided into groups of combination (n = 52) and control (n = 52) by using a random number table. Detailed information, such as gender, age, body weight, height, and medical histories, were recorded by trained physicians. Body mass index (BMI) was calculated according to the formula: BMI (kg/m^2) = weight (kg)/height $(m)^2$. Blood glucose, glycosylated hemoglobin, blood lipids, liver function, kidney function, blood, and urine routine tests were carried out by the clinical laboratory department. The clinical data, laboratory tests, and blood samples of patients with DPN were collected and analyzed.

2.2. Subjects

This study obtained approval from the medical ethics committee of Shandong Provincial Third Hospital (No. PT-2019-039). Written informed consent was obtained from the patients. The formulation of this research protocol complies with the relevant requirements of the Declaration of Helsinki of the World Medical Association. The series consisted of 30 males and 22 females, with an average age of(63.29 ± 6.39 years (range 54–78 years). The BMI range of these patients was 22.32 kg/m^2 to 26.83 kg/m^2, and the average BMI was (25.21 ± 0.23) kg/m^2. The average course of diabetes was(4.21 ± 0.27)years (range 2–9 years). The mean fasting blood glucose concentration was(6.18 ± 0.63) mmol/L (range 5.01–7.34 mmol), and the mean postprandial blood glucose concentration was(9.03 ± 0.58) mmol/L (range 7.53–10.38 mmol). The mean glycosylated hemoglobin was (7.27 ± 1.02)% (range 6.54–9.03 %).

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1)met the diagnostic criteria for diabetes according to the "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China" [9]; (2)with numbness appeared, and deep sensation or pain, temperature, and touch sensation decreased in the extremities; (3)conduction velocity of motor and sensory nerves was slowed down showed by electromyography; (4)the skin of feet was ulcerated, dry, thin, and cold diagnosed via nervous system examination; (5)tendon reflex weakened or disappeared diagnosed via tendon reflex examination.

The exclusion criteria were as follows: (1)allergic to probucol or mecobalamin tablet; (2)with malignant hypertension, malignant tumor, or critical illness; (3)with urinary system diseases or blood system diseases; (4)with abnormal functions of important organs such as heart, brain, lung, liver, and kidney; (5)with a history of drug abuse; (6)with acute complications of diabetes; (7)with severe mental disorders then could not communicate normally; (8)with other diseases that would cause abnormal sensation or movement of peripheral nerves, such as peripheral neuritis, cerebral infarction, etc.; (9)sudden accidents during treatment.

2.4. Treatment program

After admission, all patients received health education, including a healthy diet and appropriate exercise, and received routine symptomatic treatment, such as blood pressure and blood lipid control. Then both groups of patients took mecobalamin tablets [trade name: mecobalamin tablets; manufacturer: Eisai (China) Pharmaceutical Co., Ltd.; approval number: National Medicine Standard H20143107] after meals for 3 months (1 tablet/time, 3 times/d). On this basis, patients in the combination group received oral probucol tablets [trade name: probucol tablets; manufacturer: Qilu Pharmaceutical Co., Ltd.; approval number: National Medicine Standard H10980054] for 3 months (4 tablets/time, 2 times/d).

2.5. Evaluation index

Before and after treatment, the Toronto Clinical Scoring System (TCSS) [10], nerve conduction velocity, and oxidative stress indicators were tested, and the clinical efficacy and adverse reactions were counted.

TCSS: TCSS was tested as previously described in detail [11]. A doctor who specialized in neurological examinations for more than 5 years was responsible for this. Each patient was questioned about the presence or absence of pain (such as burning, stabbing, or shock-like pain), tingling, numbness, and weakness in the feet or the upper-limb; and the presence or absence of unsteadiness on ambulation. Sensory testing was tested at the first toe and rated as normal or abnormal. Each patient was asked about their sensation while their toes were stimulated by a tuning fork, light touching, needle, instrument with different temperatures, and about their joint position sensation. Nerve reflexes of two lower limbs including ankle reflex and knee reflex were tested, respectively. The clinical neuropathy score is a continuous variable ranging (range 0–19 points). Six points are derived from symptoms, five points from sensory testing distally at the toes, and eight points from lower limb reflexes. The patient with a score of 0–5 was considered no diabetic peripheral neuropathy, a score of 6–8 was considered a mild disease, a score of 9–11 was considered a moderate disease, and a score greater than 11 was considered a severe disease.

Nerve conduction velocity: sensory nerve conduction velocity (SNCV) and motor nerve conduction velocity (MNCV) of the common peroneal nerve and median nerve of each patient were tested by the ND-092 electromyography instrument produced by Shanghai Poseidon Medical Electronic Instrument Co., Ltd.

Oxidative stress indicators: All patients fasted for at least 12 h before blood samples were collected. Biochemical parameters, such as superoxide dismutase (SOD), malondialdehyde (MDA), glutathione peroxidase (GSH-Px), and catalase (CAT) were measured through enzyme-linked immunosorbent assay (ELISA) purchased from the kit produced by Shanghai Hengyuan Biotechnology Co., Ltd.

Clinical efficacy: The clinical efficacy was evaluated according to the indicators of blood glucose, blood lipid, peripheral nerve sensation,

Achilles tendon reflex, and other neuropathic symptoms, sensory conduction velocity, and motor nerve conduction velocity. Clinical efficacy is divided into remarkably effective, effective, and ineffective. Remarkably effective: blood glucose and blood lipid indicators were restored to normal, peripheral nerve sensation was normal, Achilles tendon reflexes and other neuropathic symptoms disappeared, motor nerve conduction velocity and sensory conduction velocity increased by more than 2 m/s; Effective: blood glucose and blood lipid indicators were significantly reduced, Achilles tendon reflexes and other neuropathic symptoms reduced a lot, motor nerve conduction velocity and sensory conduction velocity increased by more than 1 m/s; Ineffective: the indicators of blood glucose, blood lipid, peripheral nerve sensation, Achilles tendon reflex, and other neuropathic symptoms, sensory conduction velocity and motor nerve conduction velocity had no significant change or aggravated. Total effective rate = remarkable efficiency rate + effective rate.

Adverse reactions: Observe whether all patients had gastrointestinal discomfort, skin itching, and other symptoms during the treatment. Monitor the changes in the patients' liver function, kidney function, blood, and urine routine before and after treatment.

2.6. Statistical analysis

Software SPSS 21.0 were used for data analysis. Measurement data were expressed as means ± standard deviation (SD). Repeated measures analysis of variance was used to compare the data of each group as a whole, and a *t*-test was used to compare the data between and within groups. Normality was checked for all data before analysis. Count data were expressed as a rate (%) and compared by the $\chi 2$ test. A *p*-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. General Data of the two groups

No statistical difference was found in age, gender, BMI, course of diabetes, fasting blood glucose concentration, postprandial blood glucose concentration, or mean glycosylated hemoglobin between the two groups ($p > 0.05$). The combination group consisted of 30 males and 22 females with a mean age of 63.8 ± 6.39 years. The BMI range of this group patients was 22.32 kg/m^2 to 26.83 kg/m^2, and the average BMI was 25.21 ± 0.23 kg/m^2. The average course of diabetes in this group was 4.21 ± 0.27 years (range 2–9 years). The mean fasting blood glucose concentration of the combination group was 6.18 ± 0.63 mmol/L (range 5.01–7.34 mmol/L), and the mean postprandial blood glucose concentration was 9.03 ± 0.58 mmol/L (range 7.53–10.38 mmol/L). The mean glycosylated hemoglobin of this group was 7.27 ± 1.02 % (range 6.54–9.03 %). The control group consisted of 31 males and 21 females with a mean age of 63.23 ± 6.16 years. The BMI range of this group patients was 22.26–26.79 kg/m^2, and the average BMI was 25.19 ± 0.25 kg/ m^2. The average course of diabetes in this group was 4.19 ± 0.21 years (range 2–9 years). The mean fasting blood glucose concentration of this group was 6.21 ± 0.65 mmol/L (range 4.92–7.36 mmol/L), and the mean postprandial blood glucose concentration was 9.04 ± 0.59 mmol/L (range 7.49–10.42 mmol/L). The mean glycosylated hemoglobin of this group was 7.23 ± 1.01 % (range 6.51–9.01%) (Table 1).

Table 1
General Data of Patients in Two Groups.

variable	combination groups	control groups	*p*
number of patients	52	52	
Gender			0.842
Male	30	31	
Female	22	21	
Mean age(yr)	63.29 ± 6.39	63.23 ± 6.16	0.961
BMI(kg/m2)	25.21 ± 0.23	25.19 ± 0.25	0.672
Course of diabetes(yr)	4.21 ± 0.27	4.19 ± 0.21	0.674
Fasting blood glucose concentration (mmol/L)	6.18 ± 0.63	6.21 ± 0.65	0.812
Postprandial blood glucose concentration(mmol/L)	9.03 ± 0.58	9.04 ± 0.59	0.931
Glycosylated hemoglobin(%)	7.27 ± 1.02	7.23 ± 1.01	0.841

BMI: body mass index.

3.2. TCSS Scores of patients in the two groups

There was no significant difference in the symptom scores, sensory scores, reflex scores, and total scores between the two groups before treatment ($p > 0.05$), while these four indicators of the combination group were significantly lower than that in the control group after treatment ($p < 0.05$), and the indicators after treatment were significantly lower than that before treatment($p < 0.05$) (Table 2).

3.3. Nerve conduction velocity of patients in the two groups

There was no significant difference in the SNCV and NMCV of the common peroneal nerve and median nerve between the two groups before treatment($p > 0.05$), while the indicators of the combination group were significantly higher than that of the control group($p < 0.05$) after treatment and the indicators of the two groups after treatment were significantly higher than that before treatment($p < 0.05$) (Table 3).

3.4. Assessment of oxidative stress of patients in the two groups

Before treatment, there was no significant difference in SOD, MDA, GSH-Px, or CAT between the two groups ($p > 0.05$). After treatment, the SOD, GSH-Px, and CAT in the combination group were significantly higher than that in the control group, while the MDA in the combination group was significantly lower than that in the control group ($p < 0.05$). After treatment, the SOD, GSH-Px, and CAT in the two groups were significantly higher than that before treatment, while MDA was lower (Table 4).

3.5. Clinical efficacy of patients in the two groups

The clinical efficacy of the combination group was significantly better than that of the control group (94.23 % vs 78.85 %, $p < 0.05$) after treatment (Table 5).

3.6. Adverse reaction of patients in the two groups

During the treatment, there was 1 case of gastrointestinal discomfort in each group, 1 case of skin itching in the combination group, and 2 cases of skin itching in the control group. There was no significant difference in the incidence of total adverse reactions between the two groups (3.85 % vs 5.77 %, $p > 0.05$) (Table 6). After treatment, all patients' liver function indexes, kidney function indexes, blood, and urine routine indexes were normal.

4. Discussion

Diabetic peripheral neuropathy (DPN) is a common chronic complication of the diabetic. In the early stage, there may be no obvious symptoms, as the course of diabetes progresses, diabetic patients may have symptoms such as limb numbness, tingling, formication, and burning pain alone or together. As the onset of DPN is relatively insidious, it can lead to foot ulcers, gangrene, and even amputation, which seriously affects the life quality of patients and causes a heavy economic burden to the family and society. However, there are no specific drugs for the treatment of DPN. Therefore, it is of great significance to find a

Table 2
TCSS scores of patients in the two groups.

variable	combination groups		control groups		*p*	*p**	*p#*	*P*#*
	before treatment	after treatment	before treatment	after treatment				
symptom scores	3.53 ± 0.34	1.76 ± 0.23	3.51 ± 0.41	2.21 ± 0.45	0.811	< 0.001	< 0.001	< 0.001
sensory scores	3.26 ± 0.17	1.29 ± 0.13	3.22 ± 0.22	1.76 ± 0.24	0.360	< 0.001	< 0.001	< 0.001
reflexe scores	3.65 ± 0.19	1.67 ± 0.24	3.61 ± 0.21	2.68 ± 0.17	0.369	< 0.001	< 0.001	< 0.001
total scores	10.44 ± 0.70	4.72 ± 0.60	10.34 ± 0.84	6.65 ± 0.86	0.560	< 0.001	< 0.001	< 0.001

p: comparison of 2 groups before treatment ; *p**: comparison of 2 groups after treatment ; *p#*: comparison of before and after treatment in control group ; *p*#*: comparison of before and after treatment in the combination group.

Table 3
Nerve conduction velocity of patients in the two groups.

variable	combination groups		control groups		*p*	*p**	*p#*	*P*#*
	before treatment	after treatment	before treatment	after treatment				
SNCV(m/s)								
common peroneal nerve	39.94±2.83	44.38±2.79	40.03±2.67	42.39±2.37	0.883	< 0.001	< 0.001	< 0.001
median nerve	30.13±1.97	33.56±1.73	29.93±2.01	31.32±1.67	0.650	< 0.001	< 0.001	< 0.001
NMCV(m/s)								
common peroneal nerve	50.98±3.29	57.93±3.01	51.04±3.24	54.32±3.52	0.934	< 0.001	< 0.001	< 0.001
median nerve	39.62±2.19	44.98±3.87	40.53±2.18	42.67±1.69	0.063	< 0.001	< 0.001	< 0.001

p: comparison of 2 groups before treatment ; *p**: comparison of 2 groups after treatment ; *p#*: comparison of before and after treatment in control group ; *p*#*: comparison of before and after treatment in the combination group. SNCV: sensory nerve conduction velocity; MNCV: motor nerve conduction velocity.

Table 4
Assessment of oxidative stress of patients in the two groups.

variable	combination groups		control groups		*p*	*p**	*p#*	*P*#*
	before treatment	after treatment	before treatment	after treatment				
SOD(U/L)	69.83 ± 7.73	90.63 ± 8.73	70.18 ± 7.69	84.28 ± 3.29	0.837	< 0.001	< 0.001	< 0.001
MDA(mmol/L)	6.98 ± 0.47	4.27 ± 0.12	6.91 ± 0.42	5.37 ± 0.33	0.479	< 0.001	< 0.001	< 0.001
GSH-Px(U/mL)	3.09 ± 0.35	6.43 ± 0.62	3.12 ± 0.39	4.32 ± 0.64	0.715	< 0.001	< 0.001	< 0.001
CAT(U/mL)	101.94 ± 20.39	143.98 ± 23.29	102.31 ± 19.84	121.93 ± 21.09	0.934	< 0.001	< 0.001	< 0.001

p: comparison of 2 groups before treatment ; *p**: comparison of 2 groups after treatment ; *p#*: comparison of before and after treatment in control group ; *p*#*: comparison of before and after treatment in the combination group. SOD: superoxide dismutase, MDA: malondialdehyde, GSH-Px: glutathione peroxidase, CAT: catalase.

Table 5
Clinical efficacy of patients in the two groups.

Variable	combination groups	control groups	$\chi 2$	*p*
Remarkably effective	34	21		
Effective	15	20		
Ineffective	3	11		
Total effective(n, %)	49 (94.23)	41 (78.85)	5.283	0.022

Total effective(rate) = remarkable efficiency(rate) + effective(rate).

Table 6
Adverse reaction of patients in the two groups.

Variable	combination groups	control groups	$\chi 2$	*p*
Gastrointestinal discomfort	1	1		
Skin itching	1	2		
Total adverse reaction(n, %)	2(3.85)	3(5.77)	0.210	0.647

medication regimen for the treatment of DPN.

Liu et al. [12] reported that probucol could effectively improve retinopathy in patients with diabetic retinopathy. Nuerbia Yusufu et al. [13] have confirmed that probucol could effectively improve the condition of patients with non-proliferative diabetic retinopathy and hyperlipidemia. Recent studies [14] suggested that the combination of mecobalamin tablets and epalrestat was effective in treating patients with diabetic peripheral neuropathy. Our research results indicated that the combined application of mecobalamin tablets and probucol has a better clinical effect than using the mecobalamin tablet alone.

The TCSS scoring system is simple, accurate, time-saving, reproducible, economical, and can evaluate the severity of neuropathy [15]. Therefore, we used the TCSS scoring system to evaluate the functional status of the nervous system in patients with DPN before and after treatment. In our study, the results of the TCSS scoring system suggested that compared to the use of mecobalamin tablets alone, the combined use of probucol and mecobalamin tablets could effectively improve the nerve sensation and reflex in patients with DPN, thereby improving neuropathy and helping to restore normal function of the limbs. To further evaluate the efficacy of the combined medication, we tested the nerve conduction velocity of all patients. These results showed that the SNCV and NMCV of the common peroneal nerve and median nerve of the combination group patients were significantly improved, which were better than that of the control group patients. This suggested that the use of probucol combined with mecobalamin tablets could effectively increase the nerve conduction velocity in patients with DPN.

Due to the long-term high blood glucose state in patients with DPN, a large number of oxidation products were generated in cells. Which would trigger the oxidative stress in cells, causing a series of microchanges in cells and damaging the nerve fibers. Besides, lots of cells damaged in the nutritional blood vessels would block the microcirculation and cause insufficient blood supply for the nerve fibers, which ultimately would lead to neurocardiac damage and apoptosis [16,17].

So DPN would cause abnormal changes in oxidative stress and lipid peroxidation damage indicators, such as SOD, GSH-Px, and CAT. SOD, a kind of superoxide dismutase, is an important component of the antioxidant enzyme system in the biological system. It can induce the disproportionation reaction of superoxide anion and eliminate the toxic effects of superoxide anion, then reduce and prevent the lipid peroxidation [18,19]. GSH-Px is an important peroxide decomposing enzyme, which can regulate the synthesis of prostaglandins and eliminate peroxides. GSH-Px is often used to evaluate the body's antioxidant capacity in clinical practice [20]. CAT is a kind of enzyme scavenger, also known as catalase, and it is a binding enzyme with iron porphyrin as a prosthetic group [21,22]. MDA results from lipid peroxidation of polyunsaturated fatty acids [23]. MDA can increase the permeability of cell membranes, induce mitochondrial mutations, and cause islet cell damage [24]. The production of MDA is used as a biomarker to measure the level of oxidative stress in an organism [25,26]. Oxidative stress is an important reason for inducing pancreatic β-cell apoptosis and inhibiting insulin secretion. Effective antioxidant therapy can alleviate oxidative stress and protect the function of pancreatic β-cells [24]. Therefore, antioxidant therapy is a common strategy for the clinical treatment of diabetic peripheral neuropathy. Probucol contains phenolic hydroxyl group which is easily oxidized and has a consumption effect on oxidizing substances such as peroxy free radicals and oxygen-free radicals. At the same time, Probucol also has significant lipid-lowering, anti-oxidant, anti-inductive effects [27]. Mecobalamin tablets can induce the synthesis of neuronal axonal protein, the formation of the myelin sheath, and the regeneration of axons. It can speed up the metabolism of neurons and repair damaged nerve cells. Therefore, it can be used to improve nerve conduction velocity, thereby alleviating a series of clinical symptoms in patients with DPN, but the effect is not significant when used alone [28]. Studies by Suo [29] also showed that using probucol for patients undergoing percutaneous coronary intervention could not only reduce the MDA levels but also reduce the oxidative stress response caused by surgery. In our study, the SOD, GSH-Px, and CAT in the combination group were significantly higher than that in the control group, while the MDA in the combination group was significantly lower than that in the control group after treatment. This suggested that the combined use of probucol and mecobalamin tablets could effectively reduce oxidative stress in patients with DPN.

However, due to the small sample size included in this study, a multicenter randomized controlled study should be carried out on the base of expanding the sample size in the future. At present, we are still unclear on the specific mechanism of DPN, highlighting the significant deficiencies in the intersection study of endocrinology and pathology. Therefore, basic research scholars and clinical application research need to adopt innovative thinking and have a broad vision to achieve breakthrough progress.

5. Conclusion

In conclusion, the combined use of probucol and mecobalamin tablets in the treatment of patients with DPN had a definite effect. It could reduce the TCSS scores, restore the neurological symptoms, sensations, and reflexes, increase nerve transmission speed, and reduce oxidative stress. So it is worthy of widespread promotion.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Qingdao West Coast New Area Central Hospital. Written informed consent was obtained from all the study subjects before enrollment.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

HYP and YYG contributed to the conception and design of the study; HYP performed the experiments, collected and analyzed data; HYP and YYG wrote the manuscript; All authors reviewed and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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References

[1] D. Selvarajah, D. Kar, K. Khunti, et al., Diabetic peripheral neuropathy: advances in diagnosis and strategies for screening and early intervention, Lancet Diabetes Endocrinol. 7 (12) (2019) 938–948.
[2] M.A. Yorek, Is fish oil a potential treatment for diabetic peripheral neuropathy, Curr. Diabetes Rev. 14 (4) (2018) 339–349.
[3] K. Barrell, A.G. Smith, Peripheral neuropathy, Med. Clin. North Am. 103 (2) (2019) 383–397.
[4] Y. Cheng, J. Liu, Y. Luan, et al., *Sarm1* GeneDeficiency attenuates diabetic peripheral neuropathy in mice, Diabetes 68 (11) (2019) 2120–2130.
[5] K.G. Abdel-Wahhab, E.M. Daoud, A. El Gendy, et al., Efficiencies of Low-Level Laser Therapy (LLLT) and gabapentin in the management of peripheral neuropathy: diabetic neuropathy, Appl. Biochem. Biotechnol. 186 (1) (2018) 161–173.
[6] B. Zhang, W. Zhao, J. Tu, et al., The relationship between serum 25-hydroxyvitamin D concentration and type 2diabetic peripheral neuropathy: a systematic review and a meta-analysis, Medicine (Baltimore) 98 (48) (2019), e18118.
[7] Wang Jin-Song, Y.U. Jin-Ming, Meta-analysis d Antioxidation and restenosis prevention with probucol, Chin. J. Arteriosclerosis 16 (10) (2008).
[8] Kang Xuebing, Effect observation of zinc sulfate combined with mecobalamin on treatment of patients with diabetic peripheral neuropathy, J. Clin. Med. Pract. 21 (11) (2017).
[9] Diabetes Branch of the Chinese Medical Association, Guidelines for the prevention and treatment of type 2 diabetes in China(2017), Chin. J. Diabetes Mellitus 10 (1) (2018).
[10] Chen Ming-Yue, C.A.I. Hui-min, C.H.E.N. Jiang-Yun, et al., Diagnostic value of Michigan diabetic neuropathy score and Toronto clinical scoring system in diabetic peripheral neuropathy, Chin. Gen. Pract. 20 (4) (2017) 427–431.
[11] V. Bril, B.A. Perkins, Validation of the Toronto clinical scoring system for diabetic polyneuropathy, Diabetes Care 25 (11) (2002) 2048–2052.
[12] H. Liu, M. Cai, Effect of probucol on hemodynamics, rheology, and blood lipid of diabetic retinopathy, Exp. Ther. Med. 15 (4) (2018) 3809–3814.
[13] Nuerbiya Yusufu, Guliyaer Aini, Efficacy of probucol for patients with high blood lipid and non-proliferative diabetic retinopathy, Drug Eval. Res. 42 (03) (2019) 162–165.
[14] Huang Yingying, L.I. Lixia, et al., Efficacy of Epalrestat combined with Mecobalamin Tablets in the treatment of diabetic peripheral neuropathy, China Med. Herald 15 (20) (2018) 69–72.
[15] Bai Yajuan Sun-Min, et al., Analysis on screening value of Toronto clinical scoring system on diabetic peripheral neuropathy, Nurs. Rehab. J. 14 (5) (2015) 403–405, 409.
[16] Zohaib Iqbal, Shazli Azmi, Rahul Yadav, et al., Diabetic peripheral neuropathy: epidemiology, diagnosis, and pharmacotherapy, Clin. Ther. 40 (June (6)) (2018) 828–849.
[17] N. Çakici, T.M. Fakkel, J.W. van Neck, et al., Systematic review of treatments for diabetic peripheral neuropathy, Diabet. Med. 33 (November (11)) (2016) 1466–1476, https://doi.org/10.1111/dme.13083. Epub 2016 Feb 21.
[18] lin Li, Liu Bei yan, Curative effect of α-lipoic acid combined with mecobalamin in the treatment of diabetic peripheral neuropathy and its influence on the SOD, MDA, and AOPPs, Stroke Nerv. Dis. 027 (002) (2020) 197–199, 204.
[19] N.E. Cameron, M.A. Cotter, Effects of antioxidants on nerve and vascular dysfunction in experimental diabetes, Diabetes Res. Clin. Pract. 45 (2–3) (1999) 137–146.

[20] L.U. Liang, G.A.O. Feng, L.I.U. Zhao-Chuan, et al., Assessment of oxidative stress, adipocytokine secretion, and carotid atherosclerosis in patients with type 2 diabetes mellitus and hyperlipemia, J. Hainan Med. Univ. 22 (022) (2016) 2692–2695.
[21] H. Sepasi Tehrani, A.A. Moosavi-Movahedi, Catalase and its mysteries, Prog. Biophys. Mol. Biol. 140 (2018) 5–12.
[22] C. Glorieux, P.B. Calderon, Catalase, a remarkable enzyme: targeting the oldest antioxidant enzyme to find a new cancer treatment approach, Biol. Chem. 398 (10) (2017) 1095–1108.
[23] M.W. Davey, E. Stals, B. Panis, J. Keulemans, R.L. Swennen, High-throughput determination of malondialdehyde in plant tissues, Anal. Biochem. 347 (2) (2005) 201–207.
[24] S.C. Bunnag, Implications of microcirculation-research based information on prevention and treatment of diabetes mellitus type 2: a perspective, Clin. Hemorheol. Microcirc. 34 (1–2) (2006) 43–50.
[25] K. Moore, L.J. Roberts, Measurement of lipid peroxidation, Free Radic. Res. 28 (6) (1998) 659–671.
[26] D. Del Rio, A.J. Stewart, N. Pellegrini, A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress, Nutr. Metab. Cardiovasc. Dis. 15 (4) (2005) 316–328.
[27] D. Tanous, N. Hime, R. Stocker, Anti-atherosclerotic and anti-diabetic properties of probucol and related compounds, Redox Rep. 13 (2) (2008) 48–59.
[28] Qiu Yanling, Jiang Xiufang, Chen Shufeng, Clinical study of pentoxifylline combined with mecobalamin in the treatment of diabetic peripheral neuropathy, Modern J. Integr. Trad. Chin. Western Med. 029 (003) (2020) 264–267.
[29] X.Q. Suo, S.C. Yang, Z.H. Ma, et al., Effect of probucol on preventing contrast-induced nephropathy in patients undergoing percutaneous coronary intervention, Zhonghua Yi Xue Za Zhi 97 (41) (2017) 3234–3238.