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Trimetazidine provides protection against diabetic polyneuropathy in rats *via* modulation of soluble HMGB1

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Abstract. – OBJECTIVE: The aim of this study was to evaluate the neuroprotective efficacy of trimetazidine (TMZ) in a diabetic neuropathy model of the sciatic nerve.

MATERIALS AND METHODS: We performed intraperitoneal (IP) single-dose streptozotocin (STZ) injection for a diabetes mellitus neuropathy model in 24 rats; 8 rats were in the control group, and no chemical administration was performed. 24 diabetic rats were randomly divided into 3 groups: Group 1 rats (n = 8; diabetes and saline groups) were given 1 ml/kg saline treatment. Diabetes and trimetazidine (TMZ)-treated rats (n = 8) were given TMZ 10 mg/kg/day i.p. in Group 2. Group 3 rats were given TMZ 20 mg/kg/day by i.p. for 4 weeks. At the end of the study, EMG and inclined plane testing were used, and blood samples were taken.

RESULTS: Amplitudes of CMAP increased significantly in the TMZ treatment group when compared with the group that had been given saline treatment. The latency of CMAP was significantly shortened in the TMZ treatment group as compared to the saline treatment group. When compared to the saline treatment group, 10 mg/kg and 20 mg/kg TMZ treatment significantly reduced HMGB1, Pentraxin-3, TGF-beta, and MDA levels.

CONCLUSIONS: We demonstrated the neuroprotective effect of TMZ on diabetic polyneuropathy in rats *via* modulation of soluble HMGB1.

Key Words:
HMGB1, Diabetes mellitus, Diabetic neuropathy, Trimetazidine.

Introduction

Diabetes mellitus (DM) is a chronic, hyperglycemic, metabolic disease that results in disorders in carbohydrate, protein, and fat metabolisms due to a series of pathological processes based on genetic and immune structures, either complete or proportional insufficiency or inefficacy of insulin hormones secreted by pancreatic beta cells and produces complications in almost all organ systems. Diabetic neuropathy (DN) is among the most prevalent and chronic effects of diabetes. DN is a condition that can be clinically unsubtle or asymptomatic, is not influenced by other variables, and develops only as a consequence of diabetes mellitus. Axonal dysfunction related to metabolic factors is attributed to factors such as increased Na/K ATPase activity, reduced anaerobic glycolysis, deposition of polyols, reduced protein glycation, elevated myoinositol concentration, and neuronal ischemia due to microangiopathy[1].

High mobility group box 1 (HMGB1), a nonhistone DNA-binding molecule, was initially identified as a nuclear protein that stabilizes nucleosomes and allows DNA to bend to promote gene transcription. From that time the identification of this nuclear protein's alternate role as a latened fatal mediator in sepsis accumulating data has demonstrated that extracellularly present HMGB1 is a strong proinflammatory mediator in multiple organ systems. There are two main HMGB1 secretion paths. Instant secretion from cells that are infected by pathogenic organisms or necrotic cells constitutes passive release[2,3]. In contrast, the active secretion of HMGB1 is activated by cellular signaling pathways through the engagement of plasma membrane receptors with extrinsic products at a slower rate. Inflammatory mediators affect the rate of active release. HMGB1 release may be influenced by both early proinflammatory cytokines and late proinflammatory mediators[4,5].

Trimetazidine (TMZ) inhibits 3-ketoacyl coenzyme A thiolase (3-KAT), the final enzyme of the fatty acid dehydrogenation, hydration, oxidation, and thiolysis pathways, in a specific manner. TMZ improves mitochondrial oxygen needs, prevents ATP degradation, and restores intracellular

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acidosis and electrolyte balance. As a result, the cell is protected against calcium overloading and oxidative stress, and neutrophil infiltration is prevented. Based on these results, TMZ may be beneficial in the treatment of additional neurologic diseases, including peripheral nerve damage. Even though the hypothesis was indicated in earlier papers, there had been no acknowledgment of TMZ's effect on diabetic neuropathies[6-8].

The main purpose of the current study was to examine the efficiency of TMZ on nerve regeneration in a rat diabetic neuropathy model of the sciatic nerve.

Materials and Methods

Animals

Thirty-two adult male Wistar rats, weighing 200-210 g, were used in the study. Animals were housed in cages and maintained under standard conditions with 12 h light/dark cycles at room temperature (22 ± 2°C). They were fed a standard pellet diet and tap water *ad libitum* during the study. The protocol employed in the study was approved by the Institutional Animal Care and Ethical Committee of the University of Science (Ethical Number: l4210520). All chemicals were obtained from Sigma-Aldrich Inc., unless otherwise is indicated. Institutional and national standards for the care and use of laboratory animals were followed.

Experimental Protocol

Twenty-four rats were injected intraperitoneally (IP) with a single dose of streptozotocin (STZ) (Sigma-Aldrich, Inc.; Saint Louis, MO, USA) (60 mg/kg in 0.9% NaCl, pH 4.0 adjusted with 0.2 M sodium citrate). Eight rats were allocated to the control group (n = 8, control group) and were not administered any chemicals. Normal blood glucose levels in the control group were < 120 mg/dL. After 24 h, DM was confirmed by measuring the blood glucose levels with glucose oxidase reagent strips (Boehringer-Mannheim, Indianapolis, IN, USA). The diabetic rat had blood glucose levels of 250 mg/dl or higher. Then, 24 diabetic rats were randomly separated into three groups: Group 1 rats (n = 8; diabetes + saline group) were treated with 1 ml/kg of saline, group 2 rats (n=8) received TMZ 10 mg/kg/day i.p. and group 3 rats (n = 8) received TMZ 20 mg/kg/day of i.p. (Vastarel, 20 mg, SERVIER, Suresnes, France) for 4 weeks. At the end of this research, Electromyography (EMG) and inclined plane tests were performed. The animals were then euthanized, blood samples were obtained by cardiac puncture for biochemical analysis, and the sciatic nerve was extracted for histological investigation.

EMG was procured three times from the right sciatic nerve and stimulated supramaximally (intensity 10 V, duration 0.05 ms, frequency 1 Hz, in the range of 0.5-5,000 Hz, 40 kHz/sec sampling rate) from the Achilles' tendon using a Biopac bipolar subcutaneous needle stimulation electrode (Biopac Systems, Inc., Santa Clara, CA, USA). In the 2-3. interosseous muscle, unipolar needle electrodes were used to collect compound muscle action potentials (CMAPs) and variations in motor nerve conduction velocity (NCV). Biopac Student Lab Pro version 3.6.7 (Biopac Systems, Inc., Santa Clara, CA, USA) was used to analyze the data, distal latency, duration, and amplitude of the CMAP serving as the parameters (Figure 1). Within the EMG recordings, the rectal temperatures of the rats were measured using a rectal probe (HP Viridia 24-C; Hewlett-Packard Company, Palo Alto, CA, USA) and each rat's temperature was maintained between 36 and 37 °C using a heating pad.

Histopathological Examination of the Sciatic Nerve

Formalin-fixed sciatic nerve sections (4 μm) were stained with hematoxylen and eosine. The perineural thickness of the sciatic nerve was assessed using an Olympus C-5050 digital camera attached to an Olympus BX51 microscope.

Inclined Plane Test

Using a sliding device established by Rivlin and Tator9, we assessed the motor performance

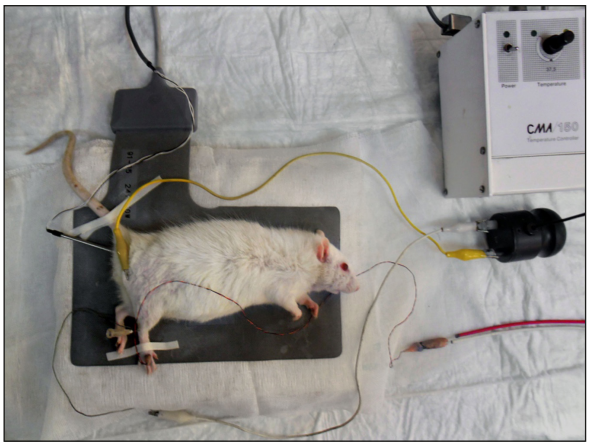

Figure 1. EMG recording system.

of rats one month following STZ administration. The device for sliding had a 50 cm X 30 cm stainless steel plane (Figure 2). The maximum angle was then established at the instant when a rat's leg slid to maintain body posture. The test was conducted three times for each head position, and the results were averaged. Each experiment was conducted following a minute-long gap.

Evaluation of Lipid Peroxidation

Plasma samples were analyzed for lipid peroxidation by detecting malondialdehyde (MDA) levels as a thiobarbituric acid reactive material (TBARS). The plasma samples were treated with trichloroacetic acid and TBARS reagent, then combined and incubated at 100°C for 60 min. The absorbance of the supernatant was measured at 535 nm following 20 min of centrifugation at 3000 rpm and chilling on ice. Tetraethoxypropane was used to calibrate MDA levels, which were represented as nM.

Measurement of Plasma TGF-β and HMGB1

Plasma pentraxin-3 (PTX3) levels were analyzed in each 100 µl sample using a PTX3 kit and a standard ELISA facility at 450 nm (Uscn Life Science Inc., Wuhan, China). PTX3 levels were measured twice in accordance with the manufacturer's instructions. The PTX3 test detection range was between 0.078 and 5 ng/ml.

Analysis of Plasma PTX3 Levels

Plasma pentraxin-3 (PTX3) levels were measured in each 100 µl sample by a standard ELISA apparatus at 450 nm using a PTX3 kit (Uscn Life Science Inc., Wuhan, China). The PTX3 levels were determined in duplicate according to the manufacturer's guide. The detection range for the PTX3 assay was 0.078 - 5 ng/ml.

Figure 2. Inclined plane test system.

Statistical Analysis

SPSS version 22.0 (IBM Corp., Armonk, NY, USA) for Windows was used for the data analysis. Student's *t*-test and analysis of variance (ANOVA) were used to compare the parametric variables, while the nonparametric variables were compared using the Mann-Whitney U test. Results were reported as the mean standard deviation of the mean (SEM). A *p*-value of less than 0.05 was considered statistically significant. $p < 0.001$ was accepted as statistically highly significant.

Results

Evaluation of Electrophysiological Records

MAP amplitudes were dramatically reduced in the diabetes + saline group. The CMAP group had a considerably longer delay than the control group. The CMAP amplitudes were considerably enhanced in the TMZ treatment group. CMAP latency was significantly decreased in the TMZ group compared with the saline group (Figure 3 and Table I).

Inclined Plane Test and Nerve Motor Function Results

At the end of the research, we assessed motor performance using an inclined plane test. In contrast to the control group, the diabetes + saline group performed this assignment inadequately. Significantly poorer mean climbing angles were recorded in the saline group compared with the control group. The rats in the TMZ 10 mg/kg and TMZ 20 mg/kg treatment groups were capable of climbing the inclined plane at greater angles. The mean climbing angles were 53.8 ± 6.3 degrees in the diabetes + saline group, 72.5 ± 5.9 degrees in the diabetes and 10 mg/kg TMZ treatment group, and 81.2 ± 4.5 degrees in the diabetes and 20 mg/kg TMZ treatment group (Table II).

Histological Evaluation of the Sciatic Nerve

At the end of the investigation, we examined histological sections of the sciatic nerve. The DM and saline treated group showed increased perineural thickness (21.6 ± 5.1 µm), while the DM and 10 and 20 mg/kg TMZ group showed decreased perineural thickness (9.4 ± 1.1 µm,6.8 ± 1.04 µm) (Figure 4 and Table III).

Plasma-Soluble HMGB1, Pentraxin-3, TGF-Beta, and MDA Levels

Comparisons of the groups' HMGB1, pentraxin-3, TGF-beta, and MDA plasma levels are

Table I. Data are expressed as mean ± SEM.

	Control group	Diabetes and saline treatment	Diabetes and TMZ 10 mg/kg treatment	Diabetes and TMZ 20 mg/kg treatment
CMAP amplitude (mV)	13.5 ± 0.7	7.4 ± 0.5*	10.8 ± 0.2$^{\#}$	12.6 ± 0.7$^{\#\#}$
Distal latans (ms)	1.38 ± 0.06	1.8 ± 0.1*	1.54 ± 0.06$^{\#}$	1.42 ± 0.05$^{\#}$

*p<0.05 (different from control), $^{\#}p$<0.05, $^{\#\#}p$<0.01 (different from Diabetes + Saline).

displayed in Table IV. The diabetes + saline group had elevated plasma levels of HMGB1, pentraxin-3, TGF-beta, and MDA compared with the control group. Ten and 20 mg/kg TMZ treatment significantly reduced the HMGB1, pentraxin-3, TGF-beta, and MDA levels compared with the saline group (Table IV).

Discussion

In the current study, we developed a diabetic neuropathy model *via* intraperitoneal administration of streptozotocin. By reducing soluble HMGB1 levels, TMZ treatment dramatically decreased oxidative stress and neuroinflammation and decreased sciatic nerve perineural thickness. This suggests that TMZ has a neuroprotective effect on diabetic neuropathy.

TMZ is a cardioprotective agent that is primarily used to treat coronary artery disease. In prior research, TMZ has been demonstrated to be beneficial in treating diabetic rats with oxidative stress-related injuries, reperfusion-induced arrhythmia, and cardiomyopathy[10-12].

The neuroprotective and antinociceptive properties of TMZ have been demonstrated in acute global ischemia, crush damage of the sciatic nerve, and paclitaxel-induced peripheral neuropathy[13-15]; nonetheless, its effects on the peripheral nervous system continue to be investigated.

In this investigation we evaluated the levels of HMGB1, pentraxin-3, and TGF-beta. Plasma concentrations of HMGB1, pentraxin-3, and TGF-beta were elevated in the diabetes + saline group relative to the control group. Treatment with 10 and 20 mg/kg TMZ substantially decreased HMGB1, pentraxin-3, and TGF-beta levels relative to the saline group.

HMGB-1 was previously assumed to be a nuclear protein; however, it has been discovered that it acts as a proinflammatory molecule in several

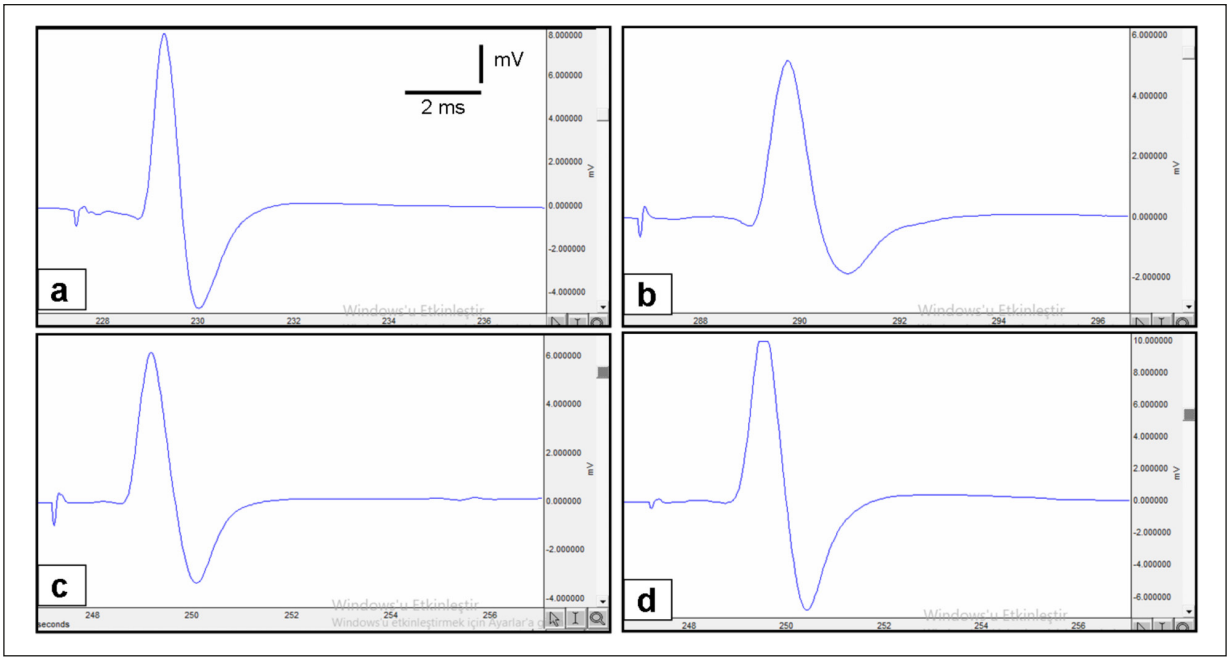

Figure 3. **a**, Control group EMG. **b**, Diabetic and saline treatment EMG. **c**, Diabetic and TMZ 10 mg/kg treatment EMG. **d**, TMZ 20 mg/kg treatment EMG.

Table II. Data are expressed as mean ± SEM.

	Control group	Diabetes and saline treatment	Diabetes and TMZ 10 mg/kg treatment	Diabetes and TMZ 20 mg/kg treatment
Maximum angle of Inclined plane test (degree)	89.1 ± 5.1	53.8 ± 6.3*	72.5 ± 5.9#	81.2 ± 4.5#
Plasma glucose (mg/dl)	81.5 ± 8.6	415.7 ± 20.3*	405.3 ± 16.9	376.6 ± 12.4#

*p<0.001 (different from control), #p<0.05 (different from Diabetes + Saline).

Table III. Data are expressed as mean ± SEM.

	Control group	Diabetes and saline treatment	Diabetes and TMZ 10 mg/kg treatment	Diabetes and TMZ 20 mg/kg treatment
Perineural thickness (µm)	3.4 ± 0.6	21.6 ± 5.1*	9.4 ± 1.1#	6.8 ± 1.04##

*p< 0.01 (different from control), #p<0.05, ##p<0.01 (different from Diabetes + Saline).

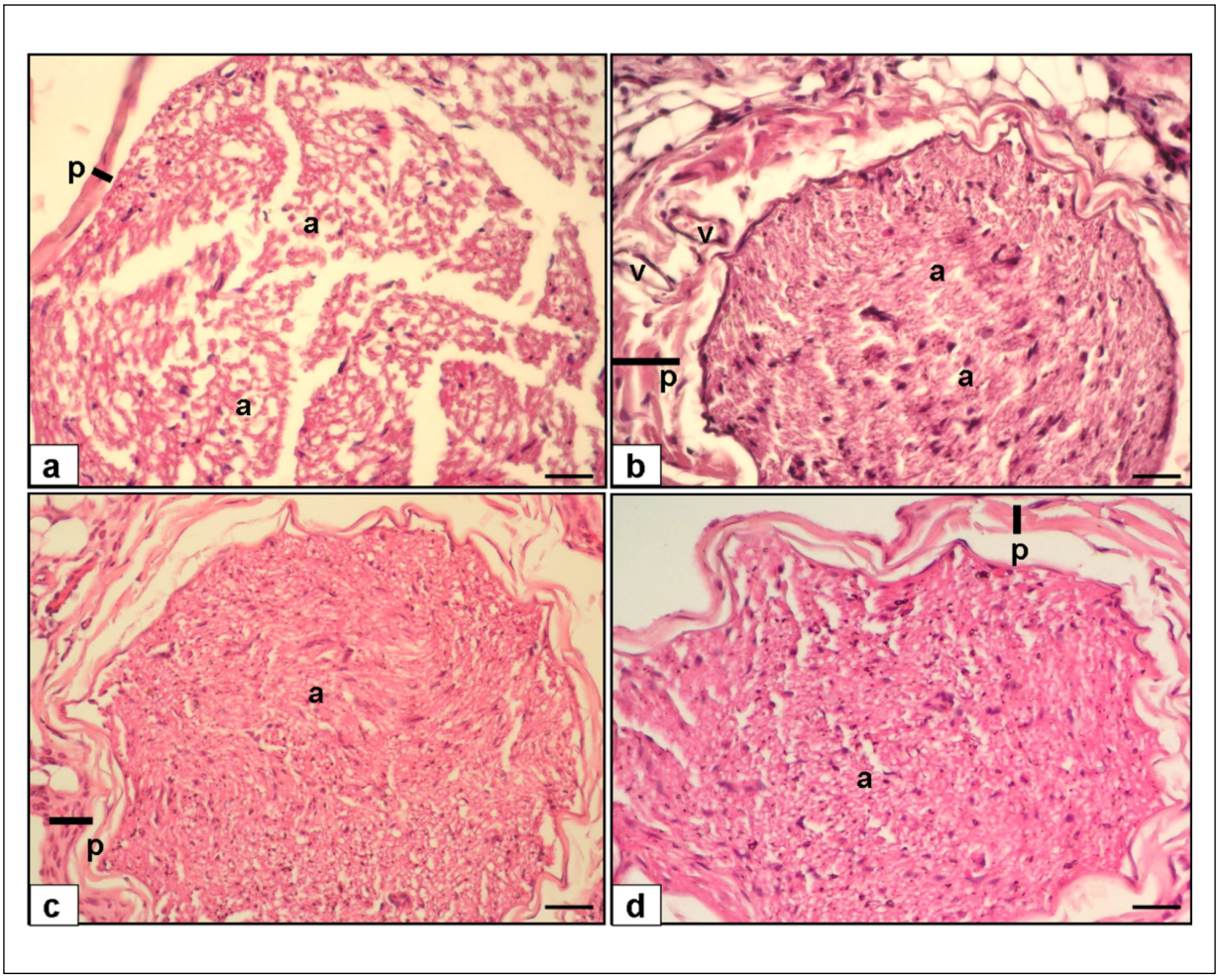

Figure 4. The histological sections of sciatic nerve. H&E staining (x 40 magnification). **a**, Control group p: perineurium and perineural thickness, a: axon. **b**, DM and saline treated group was shown increased perineural thickness. **c**, DM and 10 mg/kg TMZ Group was shown decreased perineural thickness. **d**, DM and 20 mg/kg TMZ Group was shown decreased perineural thickness.

Table IV. Data are expressed as mean ± SEM.

	Control group	Diabetes and saline treatment	Diabetes and TMZ 10 mg/kg treatment	Diabetes and TMZ 20 mg/kg treatment
Plasma soluble HMGB1 level (pg/ml)	1.05 ± 0.08	1.56 ± 0.09*	1.32 ± 0.03$^{\#}$	1.25 ± 0.06$^{\#}$
Plasma pentraxin-3 (ng/ml)	1.3 ± 0.2	3.2 ± 0.1*	2.4 ± 0.08$^{\#}$	2.07 ± 0.09$^{\#\#}$
Plasma TGF-Beta (pg/ml)	4.5 ± 0.9	22.9 ± 6.2*	16.2 ± 4.8$^{\#}$	9.5 ± 3.01$^{\#\#}$
Plasma MDA (nM)	55.1 ± 4.8	219.4 ± 18.4*	105.6 ± 9.9$^{\#}$	88.2 ± 11.5$^{\#\#}$

*p< 0.01 (different from control), $^{\#}p$<0.05, $^{\#\#}p$<0.01 (different from Diabetes + Saline).

organs. In addition to its passive release from necrotic cells, HMGB-1 is actively released in response to inflammatory signals[16]. According to accumulating evidence, HMGB1 is not only a nuclear protein but also a crucial mediator in inflammatory response. Following the stimulus, HMGB1 can be released either actively or passively into the extracellular space. The latest evidence shows that HMGB1 might be released under circumstances such as oxidative stress. In diabetes, it has been observed that hyperglycemia not only induces oxidative stress directly but also contributes to an increase in aldose reductase activity, hypoxia, and ischemia of the nerve, protein kinase C action, and insulin-like growth factor deficiency. All of these pathogenic mechanisms merge to generate significant oxidative stress[17,18]. DN, the leading reason for peripheral neuropathy, is a common chronic complication of DM type 2, and in certain circumstances, it may be accompanied by neuropathic pain.

In a paper investigating the role of HMGB1 in mechanical allodynia in a mouse diabetes type 2 model, the establishment of mechanical allodynia in mice was associated with the amplification of HMGB1 protein in the medulla spinalis. These findings lead to the theory that a positive feedback circuit exists between HMGB1 and proinflammatory cytokines, which may amplify the effect of HMGB1 on diabetic pain and make it more difficult to treat with current therapeutic interventions. Furthermore, the analgesic impact of dose- and time-dependent HMGB1 blockades might ensure a potential therapy for DM-related neuropathic pain[2,19].

Pentraxin-3 (PTX-3) is a soluble structure recognition receptor that is delivered at the site of inflammation by mononuclear phagocytes, fibroblasts, myeloid, dendritic granulosa, mesangial, endothelial, smooth muscle, and adipocyte tissues. Consequently, its level may demonstrate vascular inflammation more directly. During the inflammatory process, the vascular wall generates an abundance of PTX-3, which acts as an endothelial moderator when thrombosis and ischemic vascular disease adhere to angiogenic fibroblast growth factor-2, thereby limiting angiogenesis and restenosis. In a recent study[20], researchers showed a favorable correlation between PTX-3 and the prevalence of DM and HgA1C. Persistent hyperglycemia increased the serum concentration of PTX-3, implying that it is accurately modulated by plasma glucose levels. Notwithstanding, available data on PTX-3 as a prognostic marker of vascular inflammation is inadequate; its significance and role are still debatable and require more research[21-23].

TGF-β, a polypeptide growth factor, plays a crucial role in matrix formation, apoptosis, fibroblast differentiation, and cell proliferation]. On the other hand, clinical evidence suggests that hyperglycemia inhibits the production of TGF-β, which downregulates the synthesis of myofibroblasts from fibroblasts, hindering wound healing[24,25]. According to a recent study[26], TGF- is variously elevated in diabetes dorsal root ganglion (DRG) and sciatic nerve *in vivo*. Neutralizing antibody suppresses a rise in overall TGF- β protein under high glucose conditions *in vitro*. Furthermore, certain TGF-isoforms damage embryonic dorsal root ganglion neurons directly.

Plasma concentrations of MDA, a biomarker of lipid peroxidation and cell damage, have been reported to remain high initially and subsequently reduce in accordance with neuroprotective treatments[27]. In the present study to investigate TMZ's antioxidant effect on nerve repair, we assessed MDA levels and found them to be considerably lower in the TMZ treatment group when compared with the diabetes + saline treatment group.

Electromyography and nerve conduction study tests are far more often recognized assessment tools in peripheral nerve injury models. In CMAP curves derived from supramaximal stimulation, the distance between the positive and negative pe-

aks indicates the amplitude. Amplitude contains data regarding the magnitude of the responding motor fibers. By enhancing axonal regeneration and remyelinization, documented replies enhance more synchronized also produce greater amplitudes. CMAP amplitudes were elevated while the number of motor units that are innervated *via* regenerated axons increases[28,29].

In this study, we identified higher amplitudes in TMZ treatment groups when compared with the diabetes + saline group. With these findings, we demonstrated that TMZ promotes nerve regeneration and remyelination. Latency value is the interval between muscle stimulation and the initiation of muscular contraction potential. The latency value provides data on myelinization. In investigations of the rat sciatic nerve, electromyography and nerve conduction data should be collected from the interosseous muscles[29]. In this investigation, the diabetes + saline group was shown to have a prolonged latency time, as measured in the interosseous muscle plan.

Despite the fact that nerve regeneration is assessed histologically and biochemically, electromyographical functional outcomes are extremely important. In this study, we evaluated motor function using the tilt table test developed by Rivlin and Tator[9]. In the diabetes + saline group, rats showed motor functions actively at 53.8 ± 6.3°; however, in the TMZ treatment groups, rats showed their motor functions actively in the 10 mg/kg TMZ treatment group showed 72.5 ± 5.9° and 20 mg/kg TMZ treatment group showed 81.2 ± 4.5°.

Conclusions

Finally, TMZ appears to be beneficial for diabetic neuropathy. We demonstrated the neuroprotective effect of TMZ on diabetic polyneuropathy in rats *via* the modulation of soluble HMGB1. TMZ treatment significantly reduced oxidative stress and neuroinflammation by reducing soluble HMGB1 levels and decreasing sciatic nerve perineural thickness.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Acknowdlegments
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Informed Consent
Not applicable.

Ethics Approval
The protocol employed in the study was approved by the Institutional Animal Care and Ethical Committee of the University of Science (Ethical Number: 14210520). Institutional and national standards for the care and use of laboratory animals were followed.

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None.

Authors' Contributions
BEG, MAE, and OE contributed to study conception, design, and data interpretation. BEG, MAE, and OE contributed to collect data, their analysis and preparing the draft manuscript. All authors contributed to the final approval of the version to be published.

Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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