Effects of moderate exercise training and detraining on diabetic peripheral neuropathy in streptozotocin-induced diabetic rats

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Context
Exercise training programs have been shown to have prophylactic effects on diabetes-associated complications in murine models.

Objective
The present study aimed to elucidate the effect of moderate exercise training for 4 weeks and detraining for 2 weeks on diabetic peripheral neuropathy in type 1 diabetic rat model.

Materials and methods
Type 1 diabetes was induced by a single intraperitoneal injection of streptozotocin (45 mg/kg). Exercise training lasted for 4 weeks in trained group, whereas the detrained group stopped training for 2 weeks after training for 4 weeks. After 4 weeks, tail flick test latency, body weight, serum glucose, inflammatory markers, and nerve growth factor levels were measured, and the same was done in detrained diabetic rats after 2 weeks of detraining.

Results
Moderate exercise training for 4 weeks increased significantly tail flick latency and nerve growth factor levels, whereas the inflammatory markers were significantly improved compared with diabetic sedentary rats. Interestingly, the prophylactic effects of exercise training were maintained in the detrained rats after 2 weeks of detraining.

Conclusion
Our results explore the prophylactic mechanisms underlying the exercise training in diabetic peripheral neuropathy rat model and give further insights into the maintained prophylactic effects that lasted after 2 weeks of detraining.

Keywords:
diabetes mellitus, exercise, inflammation, nerve growth factor, peripheral neuropathy

Introduction
According to International Diabetes Federation, diabetes mellitus (DM) is considered a worldwide major health problem with increasing prevalence worldwide, and estimates predict that 640 million will be affected by 2040 [1]. Diabetic peripheral neuropathy (DPN) is the most common complication of DM, affecting both type 1 and type 2 diabetic patients; ~50% of the patients with diabetes have peripheral neuropathy with varying severity [2].

DPN features structural changes in the peripheral nerves, including demyelination, axonal atrophy, loss of nerve fibers, and slow regeneration of nerve fibers [3]. Unfortunately, neuropathy severely impairs the quality of life because of paresthesia, burning pain, hyperalgesia, and allodynia [4].

The etiology of DPN is believed to be a multifactorial problem; however, the accumulation of the final products of glycation, vascular dysfunction, oxidative stress and neurotrophic abnormalities is considered an important factor in the genesis of this disease [5–7].

DPN is mediated by an inflammatory process that is involved with changes in expressions of proinflammatory cytokines. A previous study revealed that the levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in the peripheral nerves and the spinal cord were significantly increased in a rat model of type 1 DM in comparison with normal rats [8].

Neurotrophins are a family of factors that regulate the growth and survival of the central and peripheral nervous systems, and they are vital for the nervous system development and function. The classic neurotrophin family consists of several molecules, and nerve growth factor (NGF) is one of this family, which is necessary for the growth and maintenance of neuron phenotypes in the peripheral nervous system. In diabetes, neurotrophin production and its supportive role is reduced and considered to play an important
role in DPN pathogenesis. Interestingly NGF administration in animal models with diabetic neuropathy has protective effects on the neurons of the peripheral nervous system, and it alleviates their neuropathic symptoms; however, the use of exogenous NGF has adverse effects such as muscle pain [9].

Current treatment options for symptomatic treatment of DPN include antidepressants and anticonvulsants. These agents are modestly effective for symptomatic relief, but they neither affect the underlying pathology nor do they slow progression of the disease, so early prevention of diabetic neuropathy is necessary to avoid such a serious complication. Daily moderate exercise is believed to be an important factor for the prevention of peripheral neuropathy, and it was reported that moderate intensity exercise is associated with the overall improvement of systemic inflammation in type 1 DM [10]. Moreover, previous studies have shown that increased physical activity can increase the trophic support in the peripheral nerves and their target tissues. NGF was reported to be increased in various segments of the nervous and muscular system as a result of exercise training [11,12]; however, the time response effects of exercise detraining on peripheral neuropathy with inflammatory related processes and neurotrophic factors have not been studied yet. Therefore, the present study was designed to evaluate the prophylactic effects of moderate exercise training and detraining against streptozotocin (STZ)-induced DPN in male Wistar albino rats by assessing various behavioral, inflammatory markers, and NGF levels in sciatic nerve.

Materials and methods
The current study was conducted at the Department of Physiology, Faculty of Medicine, Benha University. The study protocol was approved by the Local Ethical Committee, Benha Faculty of Medicine, Egypt.

Animals
The present study included 48 adult male Wistar albino rats, 6–8 weeks old, weighing 200–220 g, obtained from Faculty of Agriculture, Moshtohor, Egypt. Rats were grouped and kept in separate animal cages four rats in each, under the prevailing atmospheric conditions and room temperature. Animals had free access to food and water *ad libitum* and were maintained on normal light/dark cycle. At the end of the experiment and after collection of the samples, we got rid of the animals in the incinerator of Benha University Hospital.

Experiment design
Animals were divided randomly into six equal groups (*n*=8): groups I: control group for 4 weeks (C4), group II: diabetic sedentary group for 4 weeks (D4), group III: diabetic and trained for 4 weeks group (DT4) [13], group IV: control group for 6 weeks (C6), group V: diabetic sedentary group for 6 weeks (D6), and group VI: DT4 and then detrained for 2 weeks group (DDT).

At the end of the fourth week, animals from C4, D4, and DT4 groups were weighed, and the tail flick latency test (TFL) was performed. Then after overnight fasting, the animals were anesthetized with ether. Blood samples were collected through cardiac puncture for serum preparation and measurement of blood glucose level. The sciatic nerve on each side was exposed from the sciatic notch to the popliteal fossa, using a gluteal muscle–splitting approach, and transected at the sciatic notch proximally and at the point of trifurcation distally. Both sciatic nerves were dissected carefully [14] and placed on fine filter paper to remove any accompanying blood, and then sciatic nerves were rinsed with ice cold saline. A segment of sciatic nerve, ∼1.5 cm in length, was used for preparing the 10% w/v homogenates for biochemical estimation. Tissue homogenates were prepared in 0.1 mol/l PBS (pH 7.4). The homogenate was centrifuged at 1000 rpm for 4°C for 3 min and the supernatant was kept at −80°C and then used for biochemical analysis of inflammatory markers and NGF levels. The same was done in animals from C6, D6, and DDT groups at the end of the sixth week.

Diabetes induction
Diabetes was chemically induced by single intraperitoneal injection (45 mg/kg) of freshly prepared STZ (Sigma, St Louis, Missouri, USA) in 0.1 mol/l citrate buffered solution (pH 4.5). Control rats were injected with equal volume of 0.1 mol/l citrate buffer as a vehicle. Forty-eight hours after STZ injection, diabetes induction was confirmed by measuring fasting blood glucose level in a tail vein blood samples by ACCU-CHEK compact plus glucometer (Glucostar, Fenchem Biotek Ltd., Nanjing, China) using a glucose oxidase method. Rats with glucose level of 250 mg/dl or higher were considered as diabetic [15]. Following the induction of diabetes, rats were then kept for the next 24 h on 5% glucose solution bottles in their cages to prevent hypoglycemia owing to the immediate oxidative degeneration of β cells.

Exercise protocol
All rats were adapted to the water for 1 week that proceeded the entire experimental period, before the
beginning of the experiment. The adaptation consisted of keeping the animals in shallow water [16], 5 days/week, for 3 h/day. The purpose of the adaptation was to reduce stress without promoting physical training adaptations [17]. As rats are natural swimmers, exercise protocols without overload based on swimming are widely used [18]. After diabetes induction, animals were submitted to exercise training. The exercise trained groups swam 1 h a day, 5 days a week. This exercise protocol was selected as performed by Gobatto et al. [17] and Matsuo et al [19] demonstrated that it corresponds to moderate aerobic exercise training for rats. Exercise was performed in a swimming pool (length 100 cm, width 90 cm, depth 60 cm) containing warm tap water. In each exercise session, the eight rats of the same group were placed together in the swimming pool to perform the exercise. The duration of the first swimming exercise was limited to 15 min and increased by 15 min daily until it reached 1 h. Thus, continuous exercise (1 h) was performed from the fourth day until the end of the training period. The nonexercise-trained rats (the control, diabetic and the diabetic detrained rats during detraining period) were placed in shallow water 1 h, 5 days/week.

Tail flick test
Using a tail flick analgesia meter (Columbus, Ohio, USA), acute nociception was induced according to the described method by Sugimoto et al. [20]. In brief, the TFL of the restrained animals was determined by exposing the animal’s tail to a radiant heat source and recording the time between the tail exposure to the noxious thermal stimulus and tail withdrawal. To attain baseline intensity, each control animal was given five test trials and the intensity of the stimulus was adjusted so that TFLs would be between 4.0 and 8.0 s. At the end of baseline testing, the mean intensity level was calculated for all control animals. The mean intensity level was used for all subsequent testing of diabetic and trained rats. Controlled beam of light was focused on the distal 5 cm of the animal’s tail. For each animal, three recordings were made at an interval of 15 min; the mean value was used for statistical analysis.

Biochemical analysis
The serum was separated by centrifugation (5000 rpm for 5 min). Fasting glucose level was detected with the aid of a spectrophotometer using glucose kits (Spinreact, Spain). Sciatic nerve homogenate was used for measuring levels of TNF-α, IL-6, and IL-10 using assay enzyme-linked immunosorbent assay kits purchased from (Ray Biotech Inc., USA), according to the manufacturer’s instruction, and NGF using rat β-NGF enzyme-linked immunosorbent assay kits purchased from R&D Systems Inc. (Minneapolis, Minnesota, USA), according to the manufacturer’s instruction. The results were expressed as pg/mg protein.

Statistical analysis
All the data are presented as mean±SD. Evaluation of differences between groups was performed using one-way analysis of variance with post-hoc test (least significant difference) between groups with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). A value $P$ less than 0.05 was considered statistically significant.

Results
Effect of exercise training and detraining on tail withdrawal latency that associate diabetic peripheral neuropathy
As indicated by the tail flick test, pain threshold of the diabetic rats was significantly ($P<0.05$) decreased in diabetic sedentary groups D4 and D6 compared to control groups C4 and C6 respectively. Training for 4 weeks of diabetic rats (DT4) significantly ($P<0.05$) increased pain threshold compared to diabetic sedentary rats for 4 weeks (D4), however it was significantly ($P<0.05$) decreased compared to control group C4. Diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) also resulted in a significant ($P<0.05$) increase in pain threshold compared to diabetic sedentary rats for 6 weeks (D6), however it was significantly ($P<0.05$) decreased compared to control group C6. Interestingly there was non-significant ($P>0.05$) decrease in diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) compared to diabetic trained group for 4 weeks (DT4) (Fig. 1).

Effect of exercise training and detraining on body weight and serum glucose level that associate diabetic peripheral neuropathy
The present work revealed a significant ($P<0.05$) decrease in body weight in diabetic sedentary groups D4 and D6 compared to control groups C4 and C6 respectively. Training for 4 weeks of diabetic rats (DT4), showed a significant ($P<0.05$) decrease in body weight compared to both diabetic sedentary rats for 4 weeks (D4) and control group C4. Diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) showed a significant ($P<0.05$) decrease in body weight compared to both diabetic sedentary rats for 6 weeks (D6) and control group C6 (Table 1).

Mean fasting serum glucose levels showed a significant ($P<0.05$) elevation in diabetic sedentary groups D4 and D6 compared to control groups C4 and C6 respectively, training for 4 weeks of diabetic rats (DT4) showed non-significant ($P>0.05$) increase in glucose level compared to diabetic sedentary rats for 4 weeks.
weeks (D4) and a significant (P<0.05) increase compared to control group C4. Diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) also showed non-significant (P>0.05) increase in glucose level compared to diabetic sedentary rats for 6 weeks (D6) and a significant (P<0.05) increase compared to control group C6 (Table 1).

Effect of exercise training and detraining on inflammatory markers; tumor necrosis factor -α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10), and nerve growth factor (NGF) in sciatic nerve levels that associate diabetic peripheral neuropathy

Levels of TNF-alpha and IL-6 in sciatic nerve of diabetic sedentary groups D4 and D6 were significantly (P<0.05) increased compared to control groups C4 and C6 respectively. Training for 4 weeks of diabetic rats (DT4) significantly (P<0.05) decreased TNF-alpha and IL-6 compared to diabetic sedentary rats for 4 weeks (D4), however both were significantly (P<0.05) higher compared to control group C4. Diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) also resulted in a significant (P<0.05) decrease in the TNF-alpha and IL-6 compared to diabetic sedentary rats for 6 weeks (D6), however both were significantly (P<0.05) higher compared to control group C4. Interestingly there was non-significant elevation in TNF-alpha and IL-6 levels in diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) compared to diabetic trained group for 4 weeks (DT4) (Table 2).

Estimated levels of IL-10 in sciatic nerve of diabetic sedentary groups D4 and D6 were significantly (P<0.05) reduced compared to control groups C4 and C6 respectively. Training for 4 weeks of diabetic rats (DT4) significantly (P<0.05) increased IL-10 compared to both diabetic sedentary rats for 4 weeks (D4) and control group C4, however, diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) resulted in non-significant (P>0.05) increase in IL-10 compared to diabetic sedentary rats for 6 weeks (D6) and a significant (P<0.05) decrease compared to control group C6 and diabetic trained rats for 4 weeks (DT4) (Table 2).

Sciatic nerve NGF levels were significantly (P<0.05) reduced in diabetic sedentary groups D4 and D6 compared to control groups C4 and C6 respectively.

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Table 1 Changes in body weight and serum glucose of different experimental groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Serum glucose (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4</td>
<td>209.8±5.7</td>
<td>101.6±4.4</td>
</tr>
<tr>
<td>D4</td>
<td>163.5±4.5</td>
<td>370.9±11.1</td>
</tr>
<tr>
<td>DT4</td>
<td>155.7±3.2</td>
<td>372.7±3.8</td>
</tr>
<tr>
<td>C6</td>
<td>206.9±6.2</td>
<td>95.5±4.6</td>
</tr>
<tr>
<td>D6</td>
<td>145.5±4.9</td>
<td>380.9±5.4</td>
</tr>
<tr>
<td>DDT</td>
<td>138.9±2.1</td>
<td>382.6±2.7</td>
</tr>
</tbody>
</table>

Data are represented as mean±SD, n=8. C4, control for 4 weeks; D4, diabetic for 4 weeks; DT4, diabetic and trained for 4 weeks; C6, control for 6 weeks; D6, diabetic for 6 weeks; DDT, diabetic trained for 4 weeks then detrained for 2 weeks. *P<0.05, significant difference compared with C4. †P<0.05, significant difference compared with DT4.‡P<0.05, significant difference compared with D6.

Table 2 Changes in inflammatory markers; tumor necrosis factor α, interleukin-6, and interleukin-10, and nerve growth factor in sciatic nerve of different experimental groups

<table>
<thead>
<tr>
<th>Group</th>
<th>TNF-α (pg/mg)</th>
<th>IL-6 (pg/mg)</th>
<th>IL-10 (pg/mg)</th>
<th>NGF (pg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4</td>
<td>78.6±8.2</td>
<td>235.8±8.0</td>
<td>368.2±3.6</td>
<td>24.9±2.0</td>
</tr>
<tr>
<td>D4</td>
<td>376.4±7.6</td>
<td>856.8±20.7</td>
<td>103.6±4.6</td>
<td>12.8±0.8</td>
</tr>
<tr>
<td>DT4</td>
<td>176.1±4.4</td>
<td>428.8±21.4</td>
<td>381.0±8.1</td>
<td>20.6±0.6</td>
</tr>
<tr>
<td>C6</td>
<td>71.4±3.9</td>
<td>228.9±5.6</td>
<td>363.8±3.6</td>
<td>25.7±1.9</td>
</tr>
<tr>
<td>D6</td>
<td>385.8±8.9</td>
<td>881.4±18.5</td>
<td>100.4±1.7</td>
<td>12.0±1.1</td>
</tr>
<tr>
<td>DDT</td>
<td>184.0±8.8</td>
<td>441.3±14.4</td>
<td>102.5±6.3</td>
<td>19.3±1.0</td>
</tr>
</tbody>
</table>

Data are represented as mean±SD, n=8. C4, control for 4 weeks; D4, diabetic for 4 weeks; DT4, diabetic and trained for 4 weeks; C6, control for 6 weeks; D6, diabetic for 6 weeks; DDT, diabetic trained for 4 weeks then detrained for 2 weeks; IL-6, interleukin-6; NGF, nerve growth factor; TNF-α, tumor necrosis factor-α. *P<0.05, significant difference compared with DT4. †P<0.05, significant difference compared with C4. ‡P<0.05, significant difference compared with D4 group. §P<0.05, significant difference compared with C6.
Training for 4 weeks of diabetic rats (DT4) significantly ($P<0.05$) increased NGF compared to diabetic sedentary rats for 4 weeks (D4), however there was a significant ($P<0.05$) decrease compared to control group C4. Diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) also resulted in a significant ($P<0.05$) increase in NGF compared to diabetic sedentary rats for 6 weeks (D6), however there was a significant ($P<0.05$) decrease compared to control group C6. Interestingly there was non-significant decrease in NGF levels in diabetic rats trained for 4 weeks then detrained for 2 weeks (DDT) compared to diabetic trained group for 4 weeks (DT4) (Table 2).

**Discussion**

Early prevention of diabetic neuropathy which is considered severe and a common complication of diabetes is necessary, such a complication that could be asymptomatic at onset and seriously affects the quality of life. Exercise training is preferred as a non-pharmacological and non-invasive method for prophylaxis of several diabetes induced complications. The results of this study demonstrate the protective effects of swimming exercise on DPN of STZ-induced diabetic rats, and fortunately the maintained protective effects of exercise that lasted after 2 weeks of detraining in STZ-diabetic rats.

Experimentally induced diabetes by STZ is a well-documented animal model to explore behavioral, structural, and pathological changes associated with DPN [21]. Thermal sensitivity assessment in diabetic rats and mice was done using a number of behavioral tests, like tail flick test which is used to measure the latency or withdrawal threshold of the rat whose tail is exposed to thermal stimulation [22]. In the present study, in diabetic rats, the tail withdrawal latency was significantly shorter than that observed in control animals, indicating development of thermal hyperalgesia, this is in agreement with previous studies [21,23,24]. The increased nociceptor activity and sensitivity was explained by high blood glucose level that results in prolonged changes of pain threshold in the diabetic rats [25]. Previous studies have reported that blood glucose concentrations should be kept at a suitable level to prevent the neuropathic and microcirculatory diabetic complications [26,27]. Interestingly, exercise training for 4 weeks and exercise training for 4 weeks followed by detraining for 2 weeks significantly elevated the tail withdrawal latency compared with sedentary diabetic rats, indicating attenuated heat hyperalgesia and inhibition of peripheral neuropathic progression, however, our exercise training protocol did not influence glucose levels indicating that exercise exerts its protective effects by mechanisms rather than affecting glucose level. Likewise, these results were in agreement with previous studies [15,28–30] all of them demonstrated that physical training in insulin-dependent diabetics results in unchanged blood glucose control. Moreover, Rossi et al. [31] also reported that exercise training reduced hyperalgesia in STZ diabetic rats without affecting elevated serum glucose level.

Furthermore, induction of diabetes by STZ in rats presented weight loss in diabetic sedentary rats compared with control rats, these results are in accordance with Carrington et al. [32] who reported that all diabetic rats showed decreased body weight, and the reduction in body weight was owing to hyperglycemia, glucosuria and dehydration, hypoinsulinemia [33], increased muscle wasting and loss of tissue proteins and fat of adipose tissues for energy production [34]. In our study, exercise training didn’t inhibit weight loss, trained diabetic rats for 4 weeks showed a significant weight loss compared with sedentary diabetic rats, this is in agreement with the results of Selagzi et al. [15] who stated that swimming exercise training didn’t prevent body weight loss in diabetic exercised rats and that the body weight loss maintained even under exercise training. Exercise training promotes an increase in metabolic rate, increases lipid metabolism and reduces body fat, all of which can contribute to the maintained decreased body weight [35], in addition to the maintained state of hyperglycemia. Moreover, body weight loss was continued with the exercise training for 4 weeks followed by detraining for 2 weeks as it was a significantly reduced compared with sedentary diabetic rats.

The association between DPN development and pro-inflammatory mediators was demonstrated in the present study by observing elevated levels of TNF-α and IL-6 in the sciatic nerves. It has been known that STZ-induced diabetes release pro-inflammatory cytokines and cause activation of microglia in the dorsal horn of the spinal cord [36]. Moreover, diabetic-associated over expression of inflammatory biomarkers is recognized to provoke neural cells death and dysfunction. These results are in agreement with previous studies that demonstrated that STZ-diabetic rats showed increased levels and expression of TNF-α and IL-6 in the peripheral nerves such as sciatic nerve and spinal cord [8,30,37]. Our present study also revealed that IL-10; an anti-inflammatory mediator level in the sciatic nerves of STZ induced diabetic rats was...
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... decreased. The action or production of IL-10 has been known to be deficient in both experimental animals and human patients with type 1 DM [38]. Our swimming exercise protocol for 4 weeks revealed an improvement of the inflammatory state in the sciatic nerve of the diabetic rats, as well as attenuation of DPN that was detected by elevated tail withdrawal latency, there was a significant suppression in TNF-α and IL-6 associated with a significant increase in IL-10 levels, and these results are in agreement with Chen et al. [30] who reported that treadmill exercise training reduced the inflammation in the sciatic nerve of DPN rat model. It has been presumed that moderate-intensity aerobic activity has significant anti-inflammatory effects in STZ-induced diabetic rats [39]. Previous works have revealed that anti-inflammatory cytokines (e.g. IL-10) are upregulated, whereas proinflammatory cytokine production is downregulated during endurance exercise in rats [40,41]. The reduction in the proinflammatory cytokines (TNF-α and IL-6) was maintained in the diabetic DDT after exercise training for 4 weeks as it showed nonsignificant elevation compared with the trained diabetic group. However, IL-10 sciatic nerve levels showed nonsignificant increase in the detrained group compared with diabetic sedentary rats and a significant decrease compared with the diabetic trained rats. Interestingly, the tail withdrawal latency showed nonsignificant decrease compared with the diabetic trained rats, indicating maintained effect of the exercise for 2 weeks after exercise training for 4 weeks. The effect of exercise detraining on inflammatory markers, TNF-α and IL-10 levels, was reported in other models, as it was reported by Agarwal et al. [42] in paraventricular nucleus of hypertensive rats, where the detraining resulted in nonsignificant change in TNF-α level, whereas IL-10 level was even significantly decreased compared with trained group. Moreover, Rodrigues et al. [43] reported that the reduction of TNF-α and IL-6 levels by exercise training was maintained after 4 weeks of detraining in infarcted cardiac muscle in rats.

It has been well-documented that NGF plays a vital role in both survival and maintenance of sympathetic and sensory nerves. It plays an important neuroprotective function and causes axonal growth. Pathological condition that alters levels of NGF can lead neurons to lose their function and death [44]. Deficiency of peripheral nerve NGF has been implicated in thermal hyperalgesia, and nerve functional deficits are characteristic of early experimental diabetic neuropathy [45]. In the present study, we found decreased levels of NGF in the sciatic nerves of the diabetic animals, indicating loss of neuro-integrity and increased rate of nerve cells apoptosis. These findings are in accordance with Al-Rejaie et al. [37] who reported that NGF was significantly decreased in both serum and sciatic nerve of STZ-induced diabetic rats. Low levels of NGF could be owing to either decreased production or transport of NGF in diabetes or both, possibly as a result of hyperglycemia-induced oxidative stress [46]. In addition, autoimmunity may play a role in the NGF deficiency in diabetes by mechanisms related to immune neutralization of available NGF. There are structural and biochemical similarities between NGF and the insulin family of peptides, and it has been suggested that antibodies to insulin may cross-react with NGF and contribute to an effective reduction in NGF available to nerves, thereby contributing to the development of neuropathy [47]. In our experiment, swimming exercise training raised the sciatic nerve NGF level in the diabetic trained rats. A recent study has demonstrated that moderate exercise training can reverse the decrease of NGF expression in sensory root of sciatic nerve spinal segments of the diabetic rats [48]. NGF-elevated levels contribute even for a part to the attenuation of heat hyperalgesia in trained group, and previous studies have reported the efficacy of NGF for the treatment of peripheral nerve injury including DPN [49–51]. Fortunately, elevated NGF levels in the sciatic nerves of trained diabetic rats were preserved after 2 weeks of detraining, such maintained elevation indicating its participation together with the improvement of the inflammatory state in the prophylactic maintained effects of exercise.

**Conclusion**

The present study shows that moderate exercise training has a prophylactic effect on DPN, and this effect could be mediated even in part through reduction of the inflammation and elevation of sciatic nerve NGF levels. Moreover, this prophylactic effect could be maintained even if the training program is interrupted for 2 weeks.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**