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Original Article

Integrated Exercise and Glycemic and Peripheral Sensation Control in Diabetic Neuropathy: A Single-Blind, Randomized Controlled Trial

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Abstract

Background: Neuropathy control and management is an objective in therapeutic exercises prescribed for patients with Type 2 diabetic peripheral neuropathy. We examined the effects of 12-week integrated exercise (IE) on glycemic control and peripheral sensation criteria in patients with diabetic neuropathy. **Methods:** This study was carried out in 2019–2020 in Janan diabetic society of Najaf Abad in Iran. Based on MNSI scores, we assigned 40 patients into two equal paired random groups (control vs. IE). Pre and posttests were administered before and after three months of intervention. **Results:** Repeated measures ANOVA showed no significant interaction effect between the FBS of the groups ($P = 0.26$) but significant interaction effects were observed between the levels of 2 hrs pp G, 4 pm G, HbA1c, Diapason, Monofilament, and Thermofeel in favor of the IE group ($P < 0.05$). **Conclusions:** At the beginning of IE, we used massage and foam roller to release pain and improve blood circulation as well as sensation in the neuropathic areas. This may have helped the patients perform the aerobic and resistance exercises more easily. Therefore, better glycemic control and peripheral sensation were achieved. Verification of the long-term effects of this training strategy requires further study. Verification of the long-term effects of this training strategy requires further study.

Keywords: *Blood glucose, diabetes mellitus type 2, diabetic neuropathies, exercise therapy, Michigan neuropathy screening instrument*

Introduction

It is estimated that 552 million people will suffer from diabetes by 2030.[1] The prevalence of diabetes in Iran was 6% in 2011 and is expected to rise to 12% by 2030.[2] Diabetic neuropathy is one of the most common long-term complications of diabetes, which affects at least 40% of people with type 2 diabetes, and its prevalence rate increases with the growth of the disease and the extension of its history.[3] Diabetic neuropathy is heterogeneous and affects different parts of the nervous system. It has diverse clinical manifestations depending on the location and type of nerve fibers involved. Distal symmetrical neuropathy or diabetic poly neuropathy is the most common type of diabetic neuropathies.[4] It is characterized by the disruption of blood flow and progressive degradation of neuronal fibers, which disrupts the function of nerves from peripheral areas up to the upper areas.[5] Increased postural instability caused by impairment of the proprioception of the somatosensory system is one of the manifestations of diabetic neuropathy. Proprioception afferents that originate from the lower extremities, especially the structures around the ankle serve as the main database of the somatosensory system. In people with diabetic neuropathy, the loss or degradation of the afferents of lower extremities leads to a loss of precise sense of feedback from the lower extremity, leading to postural instability of the patients (sensory ataxia).

In later stages of diabetic neuropathy, patients complain of problems such as tingling feeling in the feet and arms, loss of sensation, imbalance, and foot ulceration which altogether increase the risk of amputation.[6] Diabetic neuropathy negatively affects proprioception and it decreases the static and dynamic stabilities of the body.[7] Subsequently, the risk of accidental falls in these patients is increased to 78% which is 1.5 times more than the risk for similar healthy individuals which is 30%.[7] Therefore, it

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seems that the diminishing of proprioception in patients with peripheral diabetic neuropathy results in a postural and functional imbalance that consequently affects the quality of their daily living activities and functions. Recent studies conducted on balance disorders caused by diabetic neuropathy have confirmed the impairment of static and dynamic stabilities.[8-11] Many studies on patients with diabetic neuropathy also showed a decrease in quality of life.[12-14]

Today, the benefits of exercise and physical activity in drug-independent control and management of type 2 diabetes have been well documented, but few studies have been conducted on the control of the symptoms of neuropathic diabetic patients by exercise. Exercise improves insulin resistance and enhances insulin sensitivity in diabetic patients.[15] Varieties of different exercise protocols have been used to reduce the imbalance-induced fall risks in diabetic neuropathic patients. These studies, more or less, reported that exercise training could improve balance indicators such as leg muscle strength, reaction time, postural sway, balance confidence, and risk of fall.[16] Meanwhile, some studies have shown that balance-strength exercises were more efficient for balance performance and functional activities.[17-19] Besides, it is reported that aerobic exercises are also effective in improving patients' performance and quality of life as well as their dynamic postural control.[16] Nevertheless, it should be noted that some diabetic patients might gradually enter the neuropathic phase of the disease and consequently suffer severe problems in their lower extremities and even find themselves unable to put their feet sole on the ground, let alone doing exercises, especially aerobic ones! Thus, this problem should be taken into consideration before the neuropathic patient faces serious problems in the lower extremities, but this is usually disregarded in many exercise protocols considered for these patients. We believe that an important part of the training and exercise programs considered for neuropathic patients should take account of their neuropathic complications, because neuropathy eliminates the tendency for physical activity, and probably causes the patient to enter the vicious circle of illness. Figure 1 shows how an appropriate exercise rehabilitation regimen can break this vicious circle which also makes our theoretical framework.

At present, it is typically recommended that aerobic exercise is the best choice to manage type 2 diabetes glycemic complications.[20,21] The existing evidence also supports this recommendation.[22] Nevertheless, we believe that aerobic exercise alone is not enough for these patients, especially in the latter stages of the disease. We believe that the exercise rehabilitation program for patients suffering from neuromuscular symptoms should be holistic, i.e., in addition to being aerobic, the program should take account of other factors such as neuropathic extremity pain control, flexibility, balance, and neuromuscular coordination.

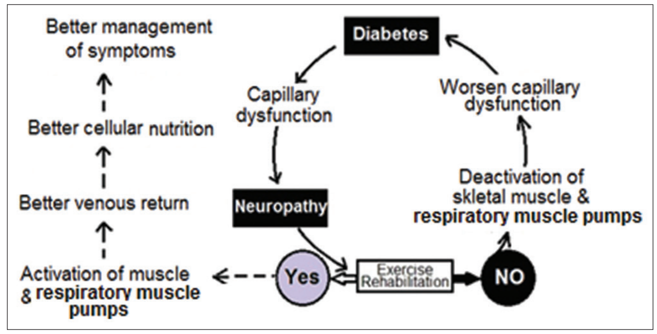

Figure 1: The vicious circle of "diabetes and Neuropathy" and the way exercise rehabilitation could break it

However, to further improve balance indicators, it is also recommended to include resistance training in the exercise program as well.[23] The National Academy of Sports Medicine (NASM) holds that corrective exercises should preferably cover the four phases self-myofascial release, lengthening, activation, and integration so that they can lead to improved pain control, flexibility, strength, and neuromuscular coordination, respectively.[24] In the present study, attempts are made to examine the extent to which an integrated exercise (IE) protocol combined with aerobic exercises and NASM exercises, outperforms a conventional aerobic exercise protocol in the management of specific problems of patients with diabetic neuropathy. In the design of the exercise protocol of the IE group, attempts are made to ensure that the selected exercises can be easily and independently done by non-athletic adults at home without any need for special or expensive equipment. In this study, we also aimed to investigate the effect of 12-week IE on four glycemic control criteria and three peripheral sensation criteria of patients with diabetic neuropathy.

Methods

The present study was a single-blind randomized control trial approved by the Ethics Board of the University of Isfahan (Ethics code: IR.UI.RCE.1397.102). All participants signed an informed consent form at the beginning of the study. A brief explanation about the participants, exercise program, exercise protocol, tests, and statistical analysis of the study follows.

Participants

The study sample consisted of 40 women aged 45–60 suffering from type 2 diabetes for over 10 years, as diagnosed by a specialist physician. The inclusion criterion was a minimum acceptable score in the Michigan Neuropathy Screening Instrument (MNSI). It includes two separate assessments: A self-administered questionnaire and an assessment of sensation.[25,26] The MNSI was administered and scored in accordance with the instructions provided by Feldman *et al*.[26] Based on MNSI scores, the participants were randomly paired and assigned to two IE and control groups (each consisting of 20 members).

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Exclusion criteria included the reluctance to continue for both groups, and medical problems hindering participation, and failure to attend more than one-third of the exercise sessions for IE group. Accordingly, the IE and the control groups had two and no participant attrition, respectively.

Exercise regimen of the IE group

The IE regimen included a 12-week indoor supervised exercise course covering three sessions of 60 to 90 minutes per week. The exercise protocol of the IE group is described in Table 1. The stated drills in the table show the maximum load/duration and they were tailored individually to fit everybody's level of physical fitness. The overall guideline was that no one should had felt pain, discomfort, or delayed onset muscle soreness during or after exercise session.

Exercise regimen of the control group

All patients attending to the diabetic rehabilitation center were clarified about the necessity of the exercise for them and instructed how to practice an outdoor unsupervised one-hour walking session, three times per week. Each session consisted of 10 minutes dynamic warming-up exercises, a long-distance 40-minute outdoor walking, and 10 minutes cooling down stretches. Moreover, they were also instructed to increase the distance of walking about five percent monthly. Every month, we interviewed the members of the control group to monitor what they do in practice, without interfering with whatever was going on. In general, all the patients tried their prescribed exercise protocol several times and then quitted it due to pain and discomfort in feet, boredom, loneliness and/or lack of energy/motivation. No one tried the exercise regimen thoroughly even for two weeks. For this, the control group is assumed as a no-exercise group, consisting of people who know exercise is essential for their health, but were unable or reluctant to do it.

Outcome measures

We used two types of outcome measures, namely blood tests and sensation tests. All tests were taken once at the

Table 1: Training Protocol of IE Group

Warm -up[1] 12 min	Self-myofascial[2] Release 8-16 min	Lengthening[3] 11 min	Activation[4] 16 min	Integration[5] 0-18 min	Cool down[6] 6 min
Walking drills (all done with elbows in half-flexed position)	Barefoot massage using foam and tennis ball Rolling	Static stretches	Balance barefoot walking with or without carrying a tray of water bottles	Combined exercises using a physio ball, step, exercise band and weight	Yoga relaxation exercises
1. Forward/backward walking with flexion-extension of arms	1. Calf forward/ backward	1. Standing hams stretch (both legs)	1. Heel to toe walk	1-2. One leg standing and ball passing between hands	1. Sama vritti breathing
2. Forward/backward walking with abduction -adduction of arms	2. Plantar fascia forward/backward	2-3. Standing calf and plantar stretch (right and left)	2. Heel to toe walk + tray	3-4. Knee cross crunch with dumbbell	2. Diaphragmatic breathing
3. Lateral walking with flexion-extension of arms	3. Plantar outside edge forward/ backward	4-5. Standing lateral hip stretch (right and left)	3. Duck feet walk	5-6. Sitting on physioball and passing a ball to a partner	3. Nadi shodhana breathing
4. Lateral walking with abduction-adduction of arms	4. Plantar inner edge forward/ backward	6-7. Standing adductor stretch (right and left)	4. Duck feet walk + tray	7-8. Sitting on physioball and raising one leg (left and right)	4. Progressive muscles relaxation
5. Forward/backward walking on the toes	5. Plantar tennis ball roll	8. Standing wide knees adductors stretch (both legs)	5. Penguin like Walk	9. Sitting on physioball and roll it back and forth	
6. Forward/backward walking on the heels	6. Ankle inversion and eversion on tennis ball	9-10. Lying hamstring stretch with band (right and left)	6. Penguin like walk + tray	10-11. Sitting on physioball and reaching right hand to left foot and vice versa	
	7. Heel pump on tennis ball	11. Towel calf stretch (both legs)	7. Ankle inversion walk	12. Heel raise on step (with weights)	
	8. Toe curl on tennis ball		8. Ankle inversion + tray		

[1,4]The time for each specific walk was 2 minutes. Depending on the ability, everybody walked specifically as long as possible, and walked normally through the rest. The length of phase specific walk was increased by %10 every two weeks. [2]Each release was performed in 5 sets (each set: 6 seconds stretch and 6 seconds rest). Stretch time was increased every two weeks by 2 sec, [3]Each stretch was performed in 5 sets (each set: 6 sec stretch and 6 sec rest). Joint is stretched to the limit of pain-free range. The ROM was slightly increased every 2 weeks, [5]Weeks 1-3, 4-6, 7-9, and 10-12 involved none, one, two, and three sets of 6-8 repetitions respectively. Each set took about 30 sec (about 15 sec workout and 15 seconds rest), [6]Each type of breathing took one minute, and relaxation took 3 min, Total time: Week one 60 min (53 mins active). Week Twelve 90 Min (79 mins active)

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beginning of the exercise program and once again at the end of the three-month exercise course. The tests were conducted by nurses who were unaware of the study group assignment. The same staff administered each test, pre- and postregimen. The detailed outcome measures follow.

2. 4.1. Blood tests included four tests of fast blood sugar (FBS), 2-hour postprandial glucose (2 hrs pp G), 4 pm glucose test (4 pm G), and hemoglobin A1c test (HbA1c). Blood tests were executed in a creditable hospital lab, and its staff had no idea about the study.

2. 4.2. Sensation outcome measures included three tests of pressure, vibration, and temperature.

Pressure sensation test

This test was carried out using a tool named monofilament. A 10-gram monofilament (GIMA, Italy) was used in the present study. Monofilament is a plastic and flexible strand that exerts a buckling force equivalent to its weight when applied on the skin. The examiner applied the monofilament strand on 10 standard foot points (refer to Figure 2) and asked the patient if they could feel the pressure. The failure to perceive monofilament pressure at three or more points was considered as a measure of sensory nerve damage.[27]

Vibration sensation test

This test was carried out using a tool named Diapason. A 128-Hz tuning fork (Sergicon, Germany) was used in the present study. Diapason is a metal tool with a handle and two prongs that vibrates when any of the two prongs are struck against a surface. After inducing vibration into the Diapason, its base was placed on the dorsum of the great toe, and the patient was asked to announce the end of the vibration perception. The interval between the announcement of the vibration end by the patient and the examiner's perception of the vibration end was used as the scoring criterion. This criterion is known as the "the absent pallesthesia interval", and the less it is, the stronger is the sense of vibration.

Figure 2: Standard points for the application of monofilament in pressure sensation test

Temperature sensation test

This test was carried out using a tool named thermofeel. A GIMA Thermofeel (made in Italy) was used in the present study. This device has two hot and cold ends that allow for the evaluation of the patient's perception of heat or cold. In this test, 10 footpoints were randomly cooled and heated, and the patient was asked to express their feelings after touch. The score was determined according to the number of correct perceptions in 10 trials.

Statistical analysis

Our measures were all continuous. Data analysis was carried out using SPSS version 23. Repeated measures analysis of variances (ANOVA) was used for inferential data analysis at the 0.05 alpha level.[28] The normality of the distribution of data was examined by the Shapiro–Wilk test. We also checked the skewness and kurtosis and visually verified the distributions by box and QQ plots.

Results

The demographic properties of the participants are presented in Table 2. As shown, there was no significant difference between the demographic properties of the groups ($P > 0.05$). Figure 3a–g show the line charts of repeated measures ANOVA on seven outcome measures of the study. In short, a significant interaction effect ($P < 0.05$) was observed between the two groups in all outcome measures in favor of the integrated group and the only exception was FBS ($P = .26$). The eta-squared (η^2) coefficient was .10, .10, and .13, respectively, for 2 hrs pp G, 4 pm G, and HbA1c measures, and it was .50, .44, and .15, respectively, for diapason, monofilament, and thermofeel sensation measures.

Discussion

Since our participants suffered from type 2 diabetes and neuropathy simultaneously, we took up a novel approach to exercise rehabilitation. We primarily focused on controlling the pain and motor impairments caused by neuropathy in the lower extremities. Without such an

Table 2: Demographic properties of the participants, compared by independent *t*-test

Factor	Mean (SD)		Student *t*-test
	C group (*n*=18)	IE group (*n*=20)	*P*
Age (years)	57.95 (4.56)	54.44 (6.12)	0.051
Weight (kg)	74.00 (8.65)	79.97 (15.74)	0.150
Height (cm)	157.45 (6.76)	158.00 (7.62)	0.814
BMI (kg/m^2)	29.93 (3.71)	32.05 (5.77)	0.182
Michigan Q (1-15)	8.10 (2.47)	8.13 (1.58)	0.965
Michigan PT (1-5)	4.48 (1.25)	4.47 (1.31)	0.981

C: Control, IE: Integrated exercises, SD: Standard deviation, Kg: Kilogram, cm: Centimeter, m: Kilogram/meter^2, BMI: Body mass index, Q: Questionnaire, PT: Physical tests

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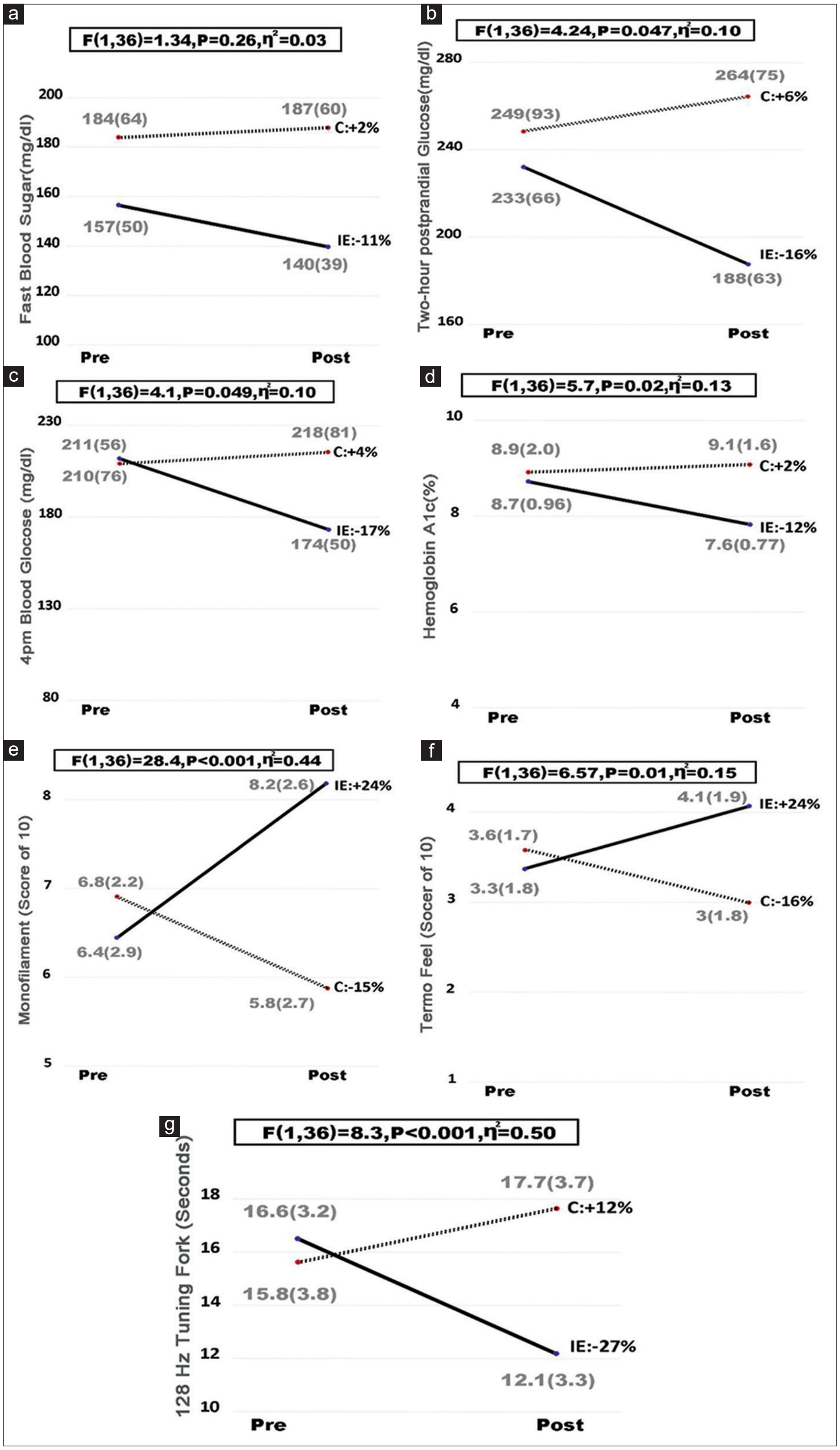

Figure 3: (a) Changes in FBS between the two groups in pre-test and post-test,n(b) Changes in 2 hrs pp G between the two groups in pre-test and post-test, (c) Changes in 4 pm G between the two groups in pre-test and post-test, (d) Changes in Hb1Ac between the two groups in pre-test and post-test, (e) Changes in monofilament between the two groups in pre-test and post-test, (f) Changes in termo feel between the two groups in pre-test and post-test, (g) Changes in 128 Hz turning Fork between the two groups in pre-test and post-test

achievement, our patients possibly were not able to engage in aerobic exercise or perform flexibility, strength, balance, and or coordination exercises within an interval of 60 to 90 minutes. Our findings showed that this novel exercise

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approach had a positive effect on both glycemic and sensation criteria. The only exception was FBS, for which no significant interaction effect was observed between the study groups.

Previous studies on neuropathic diabetic patients have mostly used aerobic exercises as the main component of the exercise protocol and used the hematological parameters as the main criteria to examine the effectiveness of the intervention. Church *et al*. examined the effects of nine months of exercise intervention on HbA1c levels. They concluded that compared to no exercise and only aerobic or only resistance training, combined exercises are much more effective.[29] Lee *et al*. also showed that in combination with a balanced exercise program, a short-term whole-body vibration therapy was beneficial in improving balance and HbA1c in elderly patients with diabetic neuropathy who are at high risk of falling.[30] Hirosaki *et al*. studied the effects of three months of once-weekly laughter and exercise program on the elderly and reported that HbA1c decreased significantly.[31] Snowling and Hopkins meta-analyzed 27 randomized controlled trials to study the effects of different modes of exercise training on the measures of glucose in diabetic elderly. They reported that all forms of exercise training produced small benefits in HbA1c and that the effects are similar to those of dietary, drug, and insulin treatments.[32]

Although the results of the abovementioned studies are similar to our findings,[29-33] it is not clear if the patients of those studies had neuropathic foot, they would have been still able to adhere to exercise protocols. Those studies did not directly address the neuropathic problems of patients in exercise protocols and did not measure the effect of training on neuropathic criteria.

In the abovementioned studies, just like our study, FBS has not improved despite improvements in glycemic criteria. It is because a variety of factors, including nutrition at night before testing, stress, and medication affect fast blood glucose. On the other hand, all participants had slept for 6 hours or more before the test, and daytime activities cannot significantly affect hematological parameters during sleep. In sleep, only the basal metabolism needs exist, and even sleep quality does not significantly affect this.

In the present study, the hematological criteria showed an 11–17% improvement in the IE group and a 2–6% deterioration in the control group. It is because the self-myofascial release exercises have inspired the IE group to develop a better attitude toward training and a better feeling toward the new condition of their lower extremities. It, in turn, might have helped them to feel livelier and more enthusiastic and to pursue their exercises and to cultivate a better attitude towards life in general. On the contrary, the neuropathic pain, aloneness, and environmental barriers might have prevented the control group from adhering to their exercise regimen. It, in turn, might have resulted in the deterioration of their hematological measures. Physical activity advice alone is not associated with improved glycemic control in type 2 diabetic patients.[33] Some other studies reported the same deterioration effects in the control group.[29,34]

In the present study, the MNSI criteria (Diapason, Monofilament, and Thermofeel) showed a 24–27% improvement in the IE group, and a 12–16% deterioration in the control group. Kluding *et al*. examined the feasibility and effectiveness of a moderately intense aerobic and resistance exercise program in people with diabetic peripheral neuropathy. They reported that the exercise intervention can improve neuropathic symptoms, nerve function, and cutaneous innervation.[35] Ahn and Song (2012) showed that Tai Chi exercises controlled neuropathic symptoms.[36] Moreover, Dixit *et al*. (2014) reported that aerobic exercises can improve neuropathic symptoms and the function of peripheral nerves.[37] The afore-mentioned outcomes are consistent with our findings. Diabetic neuropathy is a progressive chronic disorder that is accelerated by sedentary behavior, mainly because it deactivates the respiratory and muscular pumps as the only typical mechanisms of venous return. Interruption of venous return may block the blood flow into the legs, leading to tissue inflammation, exertion of increasing pressure on the capillaries, and finally blockage of their pathway. Interruption of the blood flow into the nervous system may negatively affect their nutrition and respiration and consequently lead to gradual degeneration of the nerves.

Generally speaking, in diabetic patients, arterial and capillary sclerosis may disrupt blood flow into the organ, especially in the muscles and nerves of the legs. Exercise activates the respiratory and muscular pumps and boosts blood flow to the legs. It is probably the leading cause of sensory improvements in patients. In the present study, self-myofascial release exercises and massage preceded aerobic exercises. It made this study distinguishable from previous studies. By unblocking the local veins within the legs and improving blood flow into oxygen-needing muscles, these exercises contributed to ischemia reduction and probably improved sensation and pain control. Notably, ischemia is one of the leading drivers of muscle pain.[38]

Several questions should be answered when designing exercise protocols for neuropathic patients. Is it necessary to specifically address the neuropathic foot problem? If yes, how should it be done? And if no, how do we expect that the patients still have the motive to adhere to the program for a long time, despite the pain and poor kinesthetic sense in legs? Using self-myofascial release and self-massage exercises, we managed to control the neuropathy and its consequences to some extent, without being restricted to use non-weight bearing exercises such as cycling and aquatic training.

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In the control group, the mean rate of deterioration was 4% and 15% for hematological and MNSI criteria, respectively. But why the deterioration rate in MNSI measures was so large? The hematological factors were measured objectively, while the MNSI factors were measured subjectively. The psychosocial mood of people might influence the subjective factors. The participants of the control group might have had a sense of deprivation, because they had been advised that exercise was necessary for them, but it was not feasible for them to follow their exercise regimen on their own. Research indicates that emotional stress is associated with functional impairment, poor adherence to exercise, diet and medications, and inadequate glycemic control.[39] Inversely, further to the biological advantages of physical training in a supervised exercise group, the participants of the IE group might have had a sense of psychosocial protection. It is because the exercise environment provided an opportunity for them to socialize with people like themselves, to receive attention and care, to ask their questions, to share their concerns, to trust their instructors, and to build up self-efficacy and self-confidence. In other words, besides the physical benefits of the exercise regimen, participants might have implicitly benefited from the psychosocial aspects of their exercise program. Integrating physical and mental health care can improve the outcomes for people with diabetes.[40]

Conclusions

In the present study, we found similar positive effects on quality of life, functional movements, and balance which will be reported in future articles. In general, according to the findings of the study, it can be argued that self-myofascial release exercises and self-massage prior to aerobic and resistance exercises can enhance the positive effects of exercise on neuropathic patients. In the present study, only the short-term effects of such exercises were addressed, and it is still necessary to investigate their long-term effects in further studies. Considering the positive effects of self-myofascial release exercises and self-massage on pain control, it is believed that the inclusion of these exercises at the beginning of the exercise program can increase the likelihood of having physical activity instilled into the patient's lifestyle.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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