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Structured Exercise Regimen in the Prevention of Peripheral Neuropathy in People with Type 2 Diabetes in a Low-Middle Income Country: An Open-Label, Randomized Controlled Trial

ABSTRACT

Objective: The aim of our study is to identify the role of structured exercise in the prevention of development of distal symmetric polyneuropathy (DSPN) in people with diabetes (PWD) residing in a low-middle income country (LMIC).

Materials and methods: This is an open-label, randomized, controlled trial. Subjects were randomized to standard diabetes control alone or plus a structured exercise regimen for two years. The primary outcome was the development of DSPN at the end of this period.

Results: Forty-eight patients (66.7% male) were included in the analysis (25 in intervention arm and twenty-three in control arm). The average age was 50.7 ± ± 8.5 years. Subjects in control arm received standard diabetes control with home exercise instructions while subjects in intervention arm received standard diabetes control with structured exercise for two years. The intervention group was advised to perform at least 30–60 minutes of moderate structured exercise with resistance training per week under supervision of a certified physiotherapist. The compliance rate after two years was 66.6%. Out of these patients, 21 (65.6%) were in the intervention group and 11 (34.3%) patients were in the control group. At the end of year 2, there was evidence of development of DSPN in both groups (28% in intervention arm versus 26% in control arm); however, the difference was not statistically significant.

Conclusions: This study did not show a benefit of structured exercise for neuropathy prevention in PWD residing in a LMIC. This could be related to suboptimal compliance of subjects with a structured exercise program. (Clin Diabetol 2023; 12; 6: 336–344)

Keywords: diabetes mellitus, polyneuropathy, structured exercise, prevention, low-income country

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Introduction

One of the most common microvascular complications of type 2 diabetes (T2D) and impaired glucose tolerance is distal symmetric sensorimotor polyneuropathy (DSPN) and resulting neuropathic pain [1] which contributes to significant morbidity and affects quality of life. There is some suggestion that the pres-

ence of DSPN may also increase mortality in people with diabetes (PWD) [1]. The prevalence of DSPN increases with longer duration of diabetes, low serum insulin concentrations [2], associated metabolic syndrome, smoking and depression [3].

Studies worldwide estimate the presence of DSPN anywhere from 26.7% to 50% of PWD [3–6] and 11–25% people with impaired glucose tolerance [1]. Low- and middle-income countries (LMIC) house 80% of the world's population with diabetes [7]. The prevalence of DSPN in LMICs varies greatly across countries based on the cultural setting, health practices and study population [3] with a higher prevalence in areas of lower education level and rural areas [3, 8]. A study from South India showed a prevalence of DSPN of 44.9 %, with a higher percentage in rural areas. [5]. According to the International Diabetes Federation (IDF) Diabetes Atlas (2019), 33 million Pakistanis were reported to be affected by T2D [9]. Small descriptive studies from Pakistan have estimated the prevalence of neuropathy in newly diagnosed PWD from 30% to 70% [10, 11] similar to a prevalence of 39.8% recorded from Pakistan in a multinational cohort [3]. Inadequate health education, unhealthy nutrition, insufficient health care facilities, poverty and lack of awareness compound the problem by increasing the prevalence of diabetes related complications in LMICs [12]. The presence of diabetic neuropathy is associated with substantial increase in health care cost, disability, lower productivity and depression in comparison to PWD without this complication [13].

The pathogenesis of DSPN in T2D is thought to involve oxidative stress secondary to excess free radical generation due to persistent hyperglycemia [4, 14], alterations in Schwann cell and axon transport, alterations in protein expression in the dorsal root ganglion, reduction in the production of supportive proteins, ischemia, demyelination and degeneration [15]. It follows that intensive glycemic control may be protective and may even delay or prevent development of neuropathy [16, 17].

Animal and clinical studies have reported improvement in neuropathic pain, gait imbalance and nerve function, in PWD with established neuropathy, with exercise [18–20]. There is lack of randomized controlled trials comparing a structured exercise program to routine care including non-structured exercise for prevention of diabetic neuropathy. An Italian randomized control trial conducted on 78 patients with T2D without neuropathy, demonstrated significant reduction in the development of sensory and motor polyneuropathy in the exercise group, at the end of a 4-year period of a 4 hour/week aerobic exercise regimen [21]. With improvement in metabolic parameters with exercise, one expects improvement in cutaneous reinnervation, as demonstrated by an increase in intraepidermal nerve fiber density in PWD who follow an exercise regimen; however, results have been conflicting in different studies [22, 23]. Randomized control trials have demonstrated not only improvement in electrodiagnostic parameters of an established diabetic neuropathy with exercise, but also prevention of its development with long term aerobic exercise training [24]. No trials or data is available from low- and middle-income countries related to structured exercise program in PWD.

With an established role of exercise in the prevention of development of DSPN and exercise being a readily available and cheap intervention, the current study was designed to investigate the role of a 2-year exercise regimen in the prevention of development of diabetic polyneuropathy in the Pakistani population.

Materials and methods

The study was conducted in collaboration with the Department of Neurology and Endocrinology at the Aga Khan University Hospital (AKUH), Karachi, Pakistan. Patients were recruited from January 2016 to July 2019, into this 21 month open-label, randomized, controlled trial.

Trial design

This was an open-label, randomized, controlled trial. The study was approved by the ethics review committee of AKUH, Karachi, Pakistan (IRB No: 3870-MED-ERC 15). All participants provided written informed consent for study.

Sample size

The sample size was calculated by considering a statistical power of 0.80, an α of 0.05, and effect sizes of 0.29. The resulting sample sizes were eighty--two individuals for outcomes. Therefore, we defined our sample size as eighty-two.

Inclusion criteria

All subjects fulfilling the following criteria were included: people with T2D over the age of 18 and less than 70 years, disease duration more than 5 years and less than 10 years, HbA1c $\leq$ 8.5 % on first visit and normal initial screening tests for microvascular complications (microalbuminuria and retinopathy).

Exclusion criteria

Subjects with cardiovascular, cerebrovascular, or orthopedic contraindications to exercise and signs or symptoms of peripheral neuropathy were ex-

cluded. The latter was determined after evaluation by a neurologist, screening with a validated neuropathy questionnaire, the Michigan Neuropathy Screening instrument (MNSI) [25–27], a focused neurological examination based on the Utah early neuropathy scale (UENS) [28] to screen for subclinical neuropathy and a normal initial nerve conduction studies. Those with a MNSI score (physical assessment) > 2 and/or UENS score > 4 were excluded.

Patients with type 1 or gestational diabetes, or other medical or nutritional disorders that could contribute to the development of neuropathy (other endocrine dysfunction, vitamin B12 deficiency, known autoimmune disorders, known malignancy, alcohol abuse, family history of hereditary neuropathy) and pregnant females were excluded.

Trial procedures

Participants were recruited from endocrinology clinics at Aga Khan University Hospital (AKUH), Karachi. Subjects without any symptoms suggestive of polyneuropathy and without pre-existing conditions listed in the exclusion criteria were chosen to discuss the study objectives. If they agreed, they were evaluated by a neurologist who administered the MNSI and UENS scores. Subsequently participants scoring below the limits set were recruited, after signing informed consent.

All participants underwent blood testing to screen for other etiologies that could contribute to the development of neuropathy (TSH, vitamin B12, ESR, ANA, protein electrophoresis). Those with negative screening further underwent nerve conduction studies designed to identify large fiber sensorimotor polyneuropathy, based on protocols recommended by the American Association of Neuromuscular and Electrodiagnostic medicine. (AANEM) [29] At minimum, all participants, had sural sensory and peroneal motor responses checked in a single limb, with modification of the study according to findings. In addition, medial and lateral plantar nerve responses were added to increase the sensitivity of diagnosis of distal sensory neuropathy [30, 31]. A Nicolet Viking machine was used with low- and high-pass filters set at 20 Hz and 3 kHz, respectively, with a sweep speed of 2 ms/division. All nerve stimulations were performed with a bipolar surface stimulator and NCS was performed with standard recording techniques. After recording a response, the recording electrode was moved at least twice to get the maximal response. Data were collected for the following parameters: peak latencies, amplitude, and conduction velocity. Amplitudes for the sensory nerve action potential were measured from the peak of the negative potential to the peak of the positive potential. The limb temperature was strictly maintained at > 32°C. Those with normal nerve conduction studies were enrolled in the study.

Intervention

All participants who fulfilled enrollment criteria were randomized to 1) standard diabetes control (medications + lifestyle modification) or 2) standard diabetes control with structured exercise regimen. Exercises were performed under the supervision of a certified physiotherapist (PT) (BS in physiotherapy, Masters in neuromusculoskeletal PT, working at a university hospital with 5 years' experience) who made home visits at the patient's convenience. The structured exercise program was based on the American College of Sports Medicine guidelines [32]. The intervention group was advised to perform at least 30 minutes of moderate exercise with resistance training, at least 5 days a week. The PT made home visits for participants in the intervention arm twice/month for the first 3 months and then once/month for the remaining duration of the study (21 months). On these visits, participants exercised under supervision and received instructions on how to perform the exercises at home, and a standardized International Physical Activity Questionnaire (IPAQ) was completed at each visit to ensure compliance with the exercise regimen. All participants also underwent standard initial and follow-up testing usual for all PWD, including yearly screening for retinopathy, fasting lipid panel and urine testing for microalbuminuria while HbA1c was checked every 3 months. A NCS was performed at the end of each year. Pre- and post-intervention BMI, waist circumference, blood pressure and resting heart rate were recorded.

Subjects in both groups received instructions for a standard diabetic diet by a nutritionist during their routine visits with the endocrinologist. The standard dietary advice focused on carbohydrate management, portion control, balanced meals, healthy fats, and regular meal timings. Patients were advised to restrict their simple carbohydrates and consume more complex carbohydrates that are high in fiber. However, adherence and compliance to this diet was not determined.

Randomization

A third party prepared computer-generated randomization lists. The numerical sequence was kept in opaque envelopes. The investigator opened the envelopes and proceeded to allocation of subjects. We followed simple randomization without stratification of any factors. Participants were aware of the treatment and were thus not blind to the allocation.

Exercise program

Participants in the intervention group participated in a structured exercise program based on the American College of Sports Medicine guidelines [32]. Exercises were performed under the supervision of a certified physiotherapist who made home visits at the patient's convenience. The intervention group was advised to perform at least 30–60 minutes of moderate structured exercise with resistance training per week. The physical therapist made home visits for participants in the intervention arm twice/month for the first 3 months and then once/month for the remaining duration of the study (21 months). On these visits, participants performed exercise under supervision along with instruction for self-exercise and a standardized International Physical Activity Questionnaire (IPAQ) was completed at each visit to ensure compliance with the exercise regimen.

All participants also underwent standard initial and follow-up testing usual for all PWD, including yearly screening for retinopathy, fasting lipid panel and urine testing for microalbuminuria while HbA1c was checked every 3 months. A NCS was performed at the end of each year. Pre- and post-intervention BMI, waist circumference, blood pressure and resting heart rate were recorded.

Screening tools

All participants were initially screened using the Michigan neuropathy screening instrument (MNSI) which consists of a brief questionnaire followed by a neuropathy focused examination by a medical professional. MNSI has long been considered a highly specific (95%) and sensitive (80%) test for detecting DSPN [25–27]. The MNSI *questionnaire* is self-administered. Responses are added to obtain a total score. All fifteen questions were included in the scoring algorithms. A score of > 7 was considered abnormal.

The MNSI physical assessment total possible score is 8 points and, in the published scoring algorithm, a score ≥ 2 is considered abnormal [27]. A focused neurological examination based UENS was also performed at each follow up, with a score > 4 considered abnormal [28].

Follow-up

Subjects were followed for 2 years. The endocrinologist advised standard diabetes management. Participants followed-up with the endocrinologist and nutritionist every 3 months and with the neurologist every 6 months. Follow-up with the endocrinologist was extended to 6 months if sugars were well controlled. If more frequent follow-ups were needed, they were offered free of cost. All visits to the neurologist were also free of cost.

Outcome

Primary outcome was the development of a large fiber distal symmetric diabetic polyneuropathy at the end of the trial period.

Statistical analysis

All analyses were conducted by using the Statistical package for social science SPSS (Release 19.0, standard version, copyright© SPSS; 1989-02). Data are presented either as the mean ± SD or as median, interquartile range. Variability between nerve conduction study group difference was determined by chi-square test. Continuous variables with normal distribution were analyzed using independent samples t-test. Statistical evaluation of individual patient electrophysiologic responses were subsequently determined using a Fisher's Exact Test. In all cases, $p < 0.05$ was considered statistically significant.

Results

A total of 4500 patients were pre-screened for recruitment. Of the 4500 pre-screened patients, 450 met the clinical screening criteria (Fig. 1). Of the latter, 386 individuals were not included in the final sample as they declined to consent for blood tests, nerve conduction studies and/or follow-ups. Study was conducted from December 2015 to July 2019 (Duration: 42 months).

A total of sixty-four pre-screened patients satisfying the study inclusion criteria were enrolled. Sixteen (25%) of the sixty-four patients either refused to continue in the trial or were lost to follow-up. Forty--eight participants (66.7% male) who were included in the analysis had an average age of 50.7 ± 8.5 years. Half of them had a BMI of 25 to < 30 ($n = 24$; control = 15 and intervention $n = 9$). More patients in the control group ($n = 11$) fell in the obese category with a BMI > 30. None of our recruited subjects were underweight.

There were no statistical differences in age, gender and BMI between the intervention and control groups (Tab. 1).

At initial recruitment most of our participants (42/87.5%) had a baseline MNSI score of 0 (no signs or symptoms of DSPN). Within the first year, 23% had an increase to 2–3 points in the self-reported section of the MNSI; however, this was well below the cut off of seven. 14.6% had an increase to three or greater in the physical assessment score, suggesting the development of neuropathy. However, there was no significant difference between the control and intervention arm.

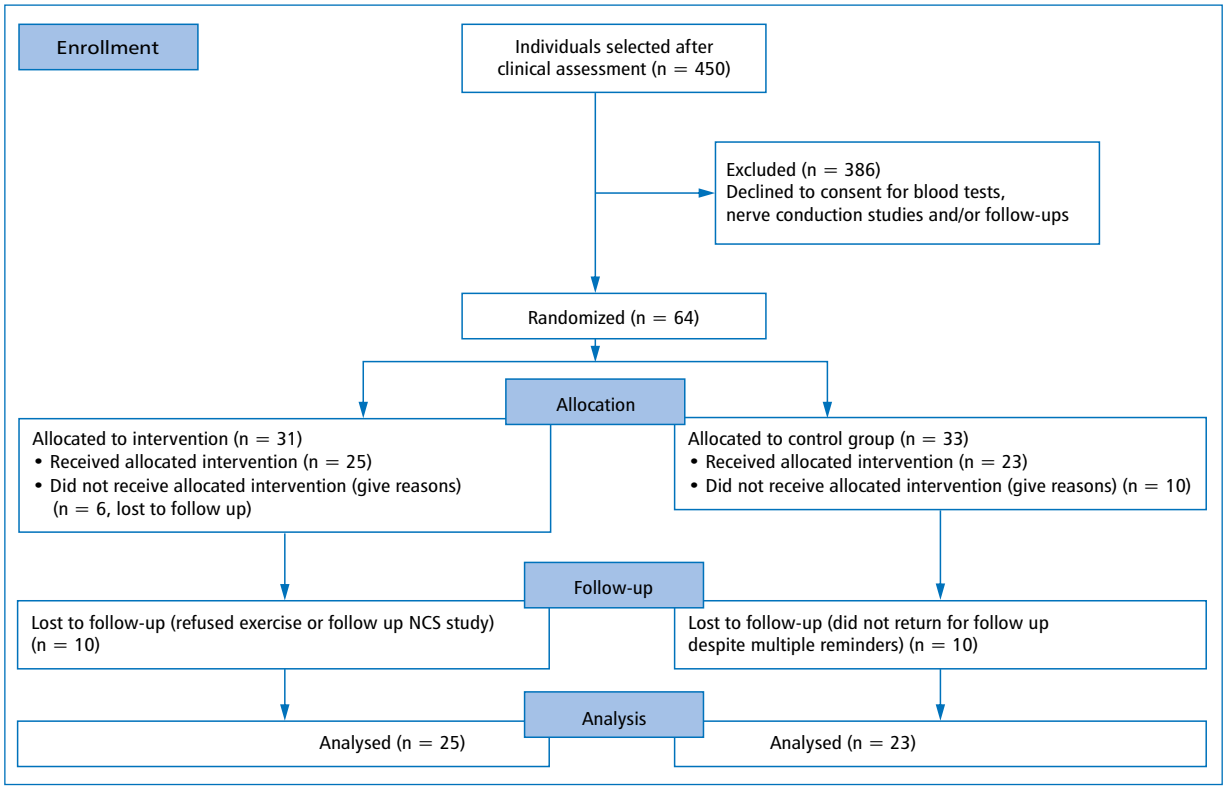

Figure 1. Flow Diagram of the Study

Table 1. Baseline Characteristics of Study Population (n = 48)

	Total	Intervention group; n = 25	Control group; n = 23	p-value
Age [years]	50.7 ± 8.5	51.0 ± 9.0	50.3 ± 8.1	0.79
Mean ± SD				
Gender				
Male	32 (66.7)	16 (64)	16 (69.6)	0.68
Female	16 (33.3)	9 (36)	7 (30.4)	
BMI [kg/m^2]				
Normal	8 (16.7)	5 (20)	3 (13)	0.12
Overweight	24 (50)	15 (60)	9 (39.1)	
Obese	16 (33.3)	5 (20)	11 (47.8)	
Employment				
Employed	29 (60.4)	16 (64)	13 (56.5)	0.59
Unemployed	19 (39.6)	9 (36)	10 (43.5)	
MNSI score physical assessment				
0–2	48 (100)	25 (100)	23 (100)	

BMI — body mass index; MNSI — Michigan Neuropathy Screening Instrument; SD — standard deviation

The UENS score that is designed to detect early sensory involvement [28] increased in both the intervention and control arms at the end of year one, in 22 and 19 subjects respectively; however, for most it remained less than the cut off of 4 (Tab. 2).

At the end of year 2 follow up, we found that 28% of the participants who had undergone a scheduled exercise regimen had developed neuropathy, based on follow up nerve conduction studies, as opposed to 26% in our control group. The difference was not con-

Table 2. Comparison of Clinical Scores for Detection of Neuropathy among Groups at Different Study Time-Points

	Total	Intervention group; n = 25 N (%)	Control group; n = 23 N (%)	p-value
MNSI score physical assessment after 1 year				
0–2	35 (85.4)	17 (77.3)	18 (94.7)	0.19
≥ 3	6 (14.6)	5 (22.7)	1 (5.3)	
MNSI physical assessment after 2 years				
0–2	23 (74.2)	17(85)	6(54.5)	0.09
≥ 3	8(25.8)	3(15)	5(45.5)	
UNES score after 1 year				
0–4	41(97.6)	22(95.7)	19(100)	0.99
> 4	1(2.4)	1(4.3)	0	
UENS score after 2 years				
0–4 normal	31(96.9)	21(100)	10(90.9)	0.34
> 4 neuropathy	1(3.1)	0	1(9.1)	
Neuropathy based on EMG findings after two years				
Normal	35 (72.9)	18 (72.0)	17 (73.9)	0.99
Neuropathy	13 (27.1)	7 (28)	6 (26.1)	
HbA1c after 1 year				
< 8.5	31 (77.5)	17 (81)	14 (73.7)	0.58
> 8.5	9 (22.5)	4 (19)	5 (26.3)	
HbA1c after 2 years				
< 8.5	31 (79.5)	16 (80)	15 (78.9)	0.93
> 8.5	8 (20.5)	4 (20)	4 (21.1)	

EMG — electromyography; HbA1c — glycated hemoglobin; MNSI — Michigan Neuropathy Screening Instrument; UENS — Utah early neuropathy scale

Table 3. Comparison of Baseline HbA1c with Follow-Up HbA1c within and between Group

	Intervention group; n = 25	Mean difference (95% CI)*	Control group; n = 23	Mean difference (95% CI)*
HbA1c Baseline	7.1 ± 0.75	–0.23(–0.68–0.20)	7.4 ± 0.71	–0.36(–0.73–0.001)
HbA1c after 1 year	7.3 ± 1.3		7.7 ± 0.98	
p-value	0.002		0.008	
HbA1c after 2 years	7.3 ± 1.2	–0.25(–0.69–0.17)	7.6 ± 0.87	–0.21(–0.62–0.19)
p-value	0.01		0.18	

*p-value > 0.05
CI — confidence interval; HbA1c — glycated hemoglobin

sidered significant. Although the difference in HbA1c levels between the two groups was not significant, the overall levels were slightly higher in the control group. Off note, the rise in HbA1c within both groups at the end of 1 year was statistically significant. (Tab. 3)

Compliance was determined by adherence to exercise regimen (as per completed international physical activity [IPAQ] questionnaire), follow up in clinic and for nerve conduction studies. Overall, the compliance rate, after one-year follow-up, was 91.6%. Among them, 23 (92%) patients were in the intervention group and 19 (82.6%) were in control group. The compliance rate after two years was 66.6%. Out of these patients, 21 (65.6%) were in the intervention group and 11 (34.3%) were in the control group.

Discussion

At baseline, our participants did not have any clinical evidence of polyneuropathy. We found that there was no significant decrease in development of polyneuropathy after following a 2-year exercise regimen with standardized treatment for diabetic control. Our study did not show a benefit of structured exercise for neuropathy prevention in PWD residing in a LMIC. Physical

activity is an easily accessible, affordable tool to control primary metabolic parameters in T2D and prevent the development of complications. However, the act relies not only on the availability of appropriate exercise and recreational facilities but also on a patient's education, interest, motivation, and self-discipline to be effective.

These findings contrast with previously published Italian randomized control trial showing benefit of exercise in preventing diabetic neuropathy [33]. Explanation for this lack of benefit may be related to suboptimal compliance with structured exercise program over two years. The patients were followed for a 2-year period due to limited funding, which may be a brief period for development of neuropathy.

In LMICs, there is great variation in the pattern of behaviors of PWD in relation to their socioeconomic status and education level [8]. Lamb et al reports that amongst the LMICs, in India and Ghana, while a higher education level led to better self-reporting of diabetes and improved control, there was a higher chance of adopting western diets and sedentary behaviors. [8] Pakistan's socioeconomic milieu and behavioral patterns are like India's population. According to a national economic survey in 2021, the literacy rate of Pakistan is 62 % with the percentage of rural population also standing at 62% [34]. These points towards low health seeking behaviors, limited access to medical care and exercise facilities, healthy diets, and lack of prioritization of physical activity.

Our study met with many limitations. Approximately 4,500 patients were screened; however, a small number of patients were enrolled (n = 48). This was primarily due to refusal to consent to the study and loss to follow up. Men were more likely to agree to be part of the study. Patients that were lost to follow up cited reasons of challenges arranging transportation to hospital for clinical follow up, unavailability of proper exercise facilities near home, unwillingness to exercise, repeated cancellation of home appointments with the physical therapist and refusal to repeat nerve conduction studies. Such participants were extensively counseled by all members of the team but remained unconvinced. In addition, the HbA1c increased in both groups over the years of study, which is a confounding factor for the development of neuropathy. Recommending exercise in PWD to prevent DSPN may not be generalizable to all populations especially in LMIC. Even amongst the latter, the pattern of health seeking behaviors and effect of socioeconomic status is variable [8]. Low income status, depression [35], lack of motivation and lack of readily available exercise facilities, gyms, walking tracks etc. all play a role in the low prioritization of exercise. However, at the same time, there is a higher prevalence [36] and greater risk of development of T2D and its complications in LMIC [37] while the total expenditure for diabetes-related health costs is 300 times less in LMIC compared to high income countries [38].

Physical activity is a low-cost intervention in prevention of T2D-related complications and expenditure. We need to focus on ways to improve acceptance of exercise and physical activity amongst the population. Encouraging patients to increase the number of steps by small increments at a time may aid in this endeavor. The current levels of exercise recommended by health professionals [39] may have a negative effect on motivation often increasing sedentary behavior and worsening unhealthy eating habits. For exercise to have an alleviating effect on diabetic complications it needs to be introduced slowly to patients to encourage relearning health. Slow re-introduction of physical activity may also aid in dispelling inertia with regards to physical activity. Most clinics taking care of PWD also offer nutrition counselling. Perhaps adding on additional counselling for the importance of an exercise regimen or combining easily accessible physical therapy venues with diabetic clinics can help improve compliance. The past several years has been flooded by the invention of devices that can record and interpret exercise events. Wearable devices have soared in popularity and carry with them the advantage of increasing time spent exercising and decreasing time spent sedentary.

Governments of LMIC need to invest in building more parks, walking tracks and recreational facilities accessible to all. Perhaps connecting these facilities with areas of worship and schools will encourage their use. Running media campaigns to inform people about the benefits of exercise and ultimate reduction in health care cost will be useful. It is a well-known fact that exercise improves control of all parameters of the metabolic syndrome and in doing so will prevent not only debilitating cerebrovascular and cardiovascular complications but also improve quality of life by prevention of development or worsening of neuropathy, retinopathy, and renal impairment, not to mention a significant reduction in final health care cost.

Article information

Ethics statement

This was an open-label, randomized, controlled trial. The study was approved by the ethics review committee of AKUH, Karachi, Pakistan (IRB No: 3870-MED-ERC 15). All participants provided written informed consent for study.

Author contributions

Sara Khan: concept, protocol writing, funding acquisition, data collection, data analysis, manuscript writing, manuscript review

Safia Awan: data collection, data analysis, manuscript writing, manuscript review

Hajra Channa: data analysis, manuscript writing, manuscript review

Asma Ahmed: concept, data collection, data analysis, manuscript writing, manuscript review

Mohammad Wasay: concept, protocol writing, data analysis, manuscript writing, manuscript review

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Conflict of interest

The authors declare that there is no conflict of interest.

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