Health, Sports & Rehabilitation Medicine
Vol. 22, no. 2, April-June 2021, 82–88

Exercises and physical procedures improve walking distance in peripheral artery disease - a randomized controlled trial

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Abstract

Background. Globally, in recent years the best methods have been sought for physical treatment, medication, revascularization in order to slow down or stop the progression of peripheral artery disease. Current treatment, along with the patient selection criteria are clearly standardized through treatment guidelines based on the results of many clinical trials.

Aims. The aim of this prospective, randomized, controlled clinical trial was to determine whether a rehabilitation program is more effective than usual care to improve ambulatory function in patients with peripheral arterial disease.

Methods. We randomized 111 patients into: the control group (which followed medication, hygienic and dietary recommendations), the exercise group, and the group with exercise and procedures. Patients were evaluated at baseline, after 12 weeks of rehabilitation and at the end of the study using the 6-minute walking distance.

Results. For both group 2 and group 3, the 6-minute walking distance values improved significantly as compared to control. We still registered after the first 12 weeks better values by 15% for the exercise group and by 18% for group 3. At the end of the study, the 6-minute walking distance values improved by 19% for the exercise group and by 22% for the group with exercises and procedures. No significant differences were found regarding the evolution of the 6-minute walking distance in females and males. The evolution of values under physical treatment is much less influenced by smoking.

Conclusions. Physical therapy is the object of more recent or older research through the great advantages it could offer in increased efficiency, low risks in relation to revascularization methods, high addressability, and lower costs.

Keywords: peripheral arterial disease, exercises, procedures, walking distance.

Introduction

While cardiovascular disease of atherosclerotic cause is the most common cause of death, chronic peripheral vascular disease, usually with a long evolution over time, is one of the most common causes of disability, thus with a negative impact on patient quality of life. Lower extremity peripheral artery disease (PAD) affects 8.5 million men and women in the United States and more than 200 million people worldwide (Benjamin et al., 2017). The number of patients with PAD is continuously increasing due to the aging population and the growing number of patients with diabetes (***, 2019).

Stage I of chronic peripheral artery disease is certainly the most favorable time to sustainably apply all means of therapy and secondary prophylaxis, but unfortunately this stage is less often found, and the patient is far from easily convinced of the future of his/her health. For this reason, stage II should not be missed either for complex assistance.

Adequate behavior of patients at home, in ordinary daily life, is more important for the evolution of the disease than most drug treatments.

Drug treatment and rehabilitation in peripheral artery disease are primarily aimed at the underlying disease and are indicated in patients whose ischemia does not threaten the integrity of the limbs, as it is not so severe as to affect their lifestyle or professional activity.

Only two medications, cilostazol and pentoxifylline, are Food and Drug Administration (FDA) approved for treating PAD-associated ischemic symptoms. However, benefits from cilostazol are modest and recent evidence suggests that pentoxifylline does not improve walking performance meaningfully more than placebo (McDermott, 2018). Cilostazol improves treadmill walking performance in people with PAD who have intermittent claudication symptoms by approximately

Received: 2021, April 22; *Accepted for publication:* 2021, April 28
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https://doi.org/10.26659/pm3.2021.22.2.82

25% to 40% (Gerhard-Herman et al., 2017).

The different means of kinetic physical therapy are the object of more recent or older research due to the great advantages they could offer: increased efficiency, low risks in relation to revascularization methods, high addressability, and lower costs (Treesak et al., 2004). By identifying the optimal exercise program to improve functional capacity, the results obtained will have substantial clinical and public health implications for millions of patients with PAD.

In 2012, a meta-analysis by Fakhry et al. summarized the results of 25 randomized clinical trials of supervised walking therapy in 1054 patients with PAD and claudication symptoms, and 15 (71%) reported between 50% and 99% improvement in maximal treadmill walking distance, while 5 (21%) reported more than 100% improvement in maximal treadmill walking distance in response to supervised walking exercise (Fakhry et al., 2012).

Gardner et al. randomized 180 participants with PAD and intermittent claudication to supervised treadmill exercise, home-based walking exercise and a control group that received light resistance training focused on the upper extremities, and demonstrated that walking exercise in a home setting significantly ameliorates the walking ability and improves the 6-min walk more than a supervised treadmill exercise program (Gardner et al., 2014).

Globally, in recent years, the best methods have been sought for physical treatment, medication, revascularization in order to slow down or stop the progression of PAD. Current treatments, along with the patient selection criteria are clearly standardized through treatment guidelines based on the results of many clinical trials. However, in Romania, the usual indication for physical therapy in patients with PAD is to walk a lot, without patients being focused at least on parameters such as intensity, duration, frequency, or without being called upon for check-ups, hence the very low compliance to this type of treatment (Pătru et al., 2020).

Hypothesis

The aim of this prospective, randomized, controlled clinical trial was to determine whether a rehabilitation program is more effective than regular medical care (medication, dietary measures) to improve outpatient function in patients with PAD and intermittent claudication.

Material and methods

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, and was approved by the Ethics Committee of the hospital. All patients provided a written informed consent.

Research protocol

a) Period and place of the research

We randomized 111 patients, 56 men and 55 women, diagnosed with PAD of the lower limbs and treated in the Physical Medicine and Rehabilitation Clinic of the Clinical Emergency County Hospital of Craiova, between February-December 2019.

b) Subjects and groups

The patients included in the study had to comply with the following inclusion criteria: diagnosis of PAD, with or without diabetes mellitus, positive Edinburgh Claudication Questionnaire, Fontaine stage IIa only (mild claudication, walking distance > 60 m), ambulatory without assistive devices, calf muscle claudication within 10 minutes of treadmill walking and calf muscle exercise. Exclusion criteria were: PAD secondary to Buerger's disease, autoimmune arteritis, fibromuscular dysplasia, chronic and repetitive occupational trauma, venous stasis, hypercoagulability disorder or arterial embolic disease, severe claudication, leg rest pain, skin ulceration, necrosis or gangrene, poorly controlled diabetes mellitus, poorly controlled hypertension, Raynaud's syndrome, exertional angina, dyspnea, fatigue or dizziness, severe coronary artery disease, congestive heart failure, exercise intolerance limited by leg pain of non-vascular origin, transmetatarsal or more proximal lower extremity amputation, unstable claudication symptoms, lower limb revascularization, major orthopedic or surgical interventions three months before the study inclusion, patient included in other current clinical studies, dementia.

Randomization was done into three groups in the order of inclusion. The control group, which throughout the study followed only the medication regimen along with hygienic and dietary recommendations (51 patients). To reduce adverse cardiovascular events associated with lower extremity PAD, our patients' treatment included modification or elimination of atherosclerotic risk factors such as: cigarette smoking, diabetes mellitus, dyslipidemia, hypertension and promotion of daily exercise and use of a non-atherogenic diet. The patients with dyslipidemia (36%) took lipid-lowering drugs (statins or fibric acid derivatives). Lifestyle interventions for PAD patients included smoking cessation, weight loss for obese patients, and intensive blood pressure and blood glucose control with antihypertensive drugs (17%) and diabetes therapies (28%). Some patients took antiplatelet therapy for reducing the risk of myocardial infarction, stroke, or vascular death, such as Aspirin 75-325 mg per day (23% patients) or Clopidogrel 75 mg per day (only 2%). Most patients took Pentoxifylline 400 mg TID (71%) and 46% patients took ginkgo biloba 120 mg per day. We encouraged proper foot care: daily foot inspection, skin cleansing, and topical moisturizing creams, urgently addressing skin lesions and ulcerations.

The exercise group (Ex group), which followed a supervised exercise programme for 12 weeks, then continued at home the exercise programme they had learnt for another 12 weeks (24 patients). The special kinesiotherapy program was easy to understand, easy to learn and especially easy to repeat at home, without requiring any special equipment. The training started with a 10-minute warm-up, consisting of exercises for mobility and respiration, followed by exercises of analytical gymnastics, Buerger gymnastics, exercises for increasing the cardiac flow and codified walking (15-60 minutes daily), ending with relaxation exercises (5-10 minutes). The exercises were chosen according to the location

of the obliterations: exercises involving the muscles of the thigh and hip were chosen for upper obliterations, exercises involving the shank muscles were performed for middle obliterations (of femoral and popliteal arteries), and exercises involving the short muscles of the leg were preferred for distal obliterations. The number of exercise repetitions was established individually, according to the physical state of every patient, these being practiced up to the onset of moderate claudication, a moment followed by a short rest in orthostatic or sitting position, until the symptoms diminished. Initially, the sessions lasted for approx. 30 minutes and the training time gradually increased with every session up to approximately 60 minutes. The kinesiotherapy sessions took place 3 times a week.

The group with exercise and procedures (Ex +P group), which during the first 12 weeks, in addition to the supervised exercise programme also followed a predetermined set of procedures of electrotherapy, hydrotherapy, thermotherapy, massage, and afterwards, during the next 12 weeks they had to continue at home the exercise programme they had learnt (36 patients). We included different forms of currents for the reflex, remote, sympatholytic, vasodilator and collateral circulation promoting effect. For example, in this prospective, double-blind, multicenter, randomized, placebo-controlled trial, transcutaneous electrical nerve stimulation (TENS) significantly delayed pain onset and increased the pain-free walking distance in one hundred subjects with unilateral PAD Leriche-Fontaine stage II (Besnier et al., 2017). Thermotherapy procedures included heat applications on the reflex areas, abdominal, low back areas, also for the sympatholytic effect. Upward trophic massage was indicated, using techniques such as effleurage, kneading.

c) Applied tests

Peripheral artery disease is a highly prevalent disease that impairs the walking ability. Apart from the walking speed, another valuable parameter in assessing the severity of claudication and also in assessing the effects of applied therapies is the walking distance.

Walking tests, such as the 6-minute walking distance (6MWD) and the 4-meter walk test, are commonly used to assess exercise endurance and ambulatory function over a short distance, respectively (Xi et al., 2017). It is a parameter that is quite easy to measure primarily because it does not require any equipment, as it is simply the quantification of the distance that a subject can cover in 6 minutes. The relevance of the recorded values is very high, because claudication occurs during the 6 minutes in most patients with PAD and they stop walking until the pain goes away while the timer continues to run. Thus, in addition to the fact that 6MWD is an important functional quality of life parameter, we can say that its measurement also contains information about the duration of claudication.

Patients were evaluated at baseline, after 12 weeks of rehabilitation and at the end of the study, after 24 weeks.

d) Statistical processing

Statistical analysis was performed using SPSS 16.0 for Windows software. Descriptive statistics including frequencies and means and correlation analysis were conducted. The Student's t-test was used to compare our scores against published norms and between different patient groups. ANOVA and Post Hoc tests were applied to compare the course of walking distance between patient groups. A p-value < 0.05 was considered statistically significant.

Results

The clinical features upon study entry and the gait features were comparable in the three groups.

In our study, most patients were males (79.27%), the average age was 69 years, with the male/female ratio being about 3.8:1; an explanation for the fact that the male/female ratio was so different is the higher prevalence of PAD in men, as it clearly appears from the literature (Song et al., 2019; Srivaratharajah & Abramson, 2018).

The distribution by age groups shows that 82% of patients with PAD, who were covered by this study, were over 60 years old, thus confirming the literature data, which indicate the age of over 60-70 years as a potential risk factor in the development of peripheral ischemia (Fowkes et al., 2017).

Regarding the education level, the distribution of patients in the three groups was approximately uniform, with most of the subjects declaring that they had secondary/higher education, followed by patients with vocational school education. Patients who had completed only primary or secondary education were the fewest and there were no significant differences between the three groups.

For the patients enrolled in the study, we obtained an average body mass index (BMI) value of 27.16 (SD = 5.2), an average that is within the ideal weight limits, but towards the upper value of these limits.

The determination of the ankle-brachial index (ABI) in the patients from the studied group allowed the calculation of an average of 0.655 (SD = 0.094), with a minimum value of 0.469 and a maximum value of 0.827. Practically equal mean and median values show a quasi-asymmetric distribution of values.

In all three groups, the mean blood pressure, both systolic and diastolic, was normal, all patients enrolled in the study were balanced in cardiovascular terms, with hypertensive subjects taking the hypotensive treatment prescribed by the cardiologist prior to the study.

The first place among the diseases most frequently associated with PAD patients was occupied in all three groups by cardiovascular and cerebrovascular diseases, including a history of myocardial infarction, heart failure, stroke, coronary heart disease, with spinal and peripheral osteoarthritis coming second in terms of comorbidity.

To identify the associated risk factors in the patients enrolled in the study, diabetes mellitus was most common, 35% in the control group, 30.4% in the exercise group and to a lesser extent, 28%, in the exercise and procedure group.

The initial features differed significantly in the group of smokers compared to non-smokers; for example, the average age of smokers was more than 2 years lower than the average age of non-smokers, the onset of claudication symptoms occurred earlier in smokers, the average ABI was 16 percent lower compared to non-smokers.

The anamnesis conducted in patients upon inclusion in the study resulted in an average duration of 4 years elapsed since the onset of claudication, with the average values of this duration in the three groups being all close to this value.

The dynamics of the values under treatment with the increase of the walking distance and even with cases recorded in which claudication did not occur during the 6 minutes were an important motivator for patients and we could see that they proved a much better compliance when measuring the walking distance compared to the walking speed. How the 6MWD values changed in the exercise group and in the exercise and other physical procedures group is shown in the following table as compared to the control group (Table I).

Table I

6MWD values per groups.

Group		N	Min	Max	Mean	SD
Control	6MWD1	51	180	250	217.55	19.431
	6MWD2	51	181	250	214.90	18.241
	6MWD3	51	188	250	224.08	19.164
	Valid N (listwise)	51				
Exercises	6MWD1	24	181	247	210.67	23.070
	6MWD2	24	225	290	253.54	20.828
	6MWD3	24	260	298	278.38	11.620
	Valid N (listwise)	24				
Exercises Procedures	6MWD1	36	180	249	215.33	20.063
	6MWD2	36	227	298	260.86	20.993
	6MWD3	36	265	315	288.94	14.491
	Valid N (listwise)	36				

As can be seen, for both group 2 and group 3, 6MWD values improved significantly compared to group 1, the control group. We still registered after the first 12 weeks higher values by 15% for the exercise group and by 18% for the exercise and procedure group. At the end of the study, after 24 weeks, 6MWD values improved by 19% for the exercise group and by 22% for the exercise and procedure group.

The following chart shows the evolution of the average 6MWD values in the three groups (Fig. 1).

Unlike the control group, in the exercise group and the exercise and procedure group, we recorded a better grouping of the values around the average at both 12 and 24 weeks.

The following chart shows the values obtained for the separate walking distance for the two genders in the three groups; no significant differences were found regarding the evolution of 6MWD in females and males (Figs. 2 and 3).

When analyzing the 6MWD parameter in smokers and non-smokers, we obtained the average values shown in the following table (Table II).

Table II

6MWD – Smoking.

Group	Smokers		N	Min	Max	Mean	SD
Control	no	6MWD1	22	180	250	216.18	18.259
		6MWD2	22	182	250	216.14	18.602
		6MWD3	22	189	250	224.95	18.464
		Valid N (listwise)	22				
	yes	6MWD1	29	181	250	218.59	20.533
		6MWD2	29	181	246	213.97	18.236
		6MWD3	29	188	250	223.41	19.978
		Valid N (listwise)	29				
Exercises	no	6MWD1	7	198	247	226.14	21.737
		6MWD2	7	249	290	266.86	17.043
		6MWD3	7	276	298	287.43	8.923
		Valid N (listwise)	7				
	yes	6MWD1	17	181	242	204.29	20.975
		6MWD2	17	225	288	248.06	20.129
		6MWD3	17	260	297	274.65	10.659
		Valid N (listwise)	17				
Exercises Procedures	no	6MWD1	14	194	246	221.36	17.394
		6MWD2	14	240	297	267.93	20.243
		6MWD3	14	271	313	292.21	13.360
		Valid N (listwise)	14				
	yes	6MWD1	22	180	249	211.50	21.071
		6MWD2	22	227	298	256.36	20.546
		6MWD3	22	265	315	286.86	15.094
		Valid N (listwise)	22				

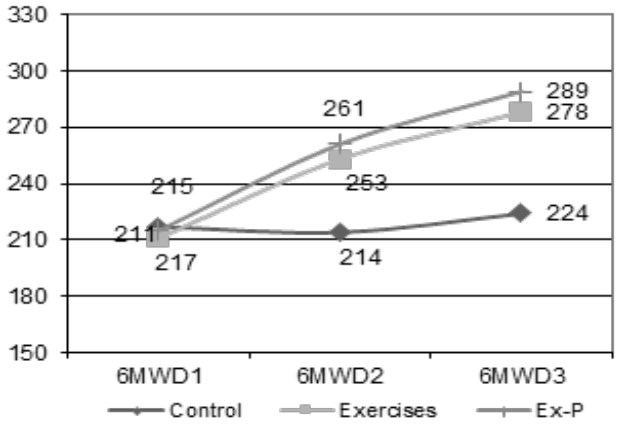

Fig. 1 – The evolution of average 6MWD values in the three groups.

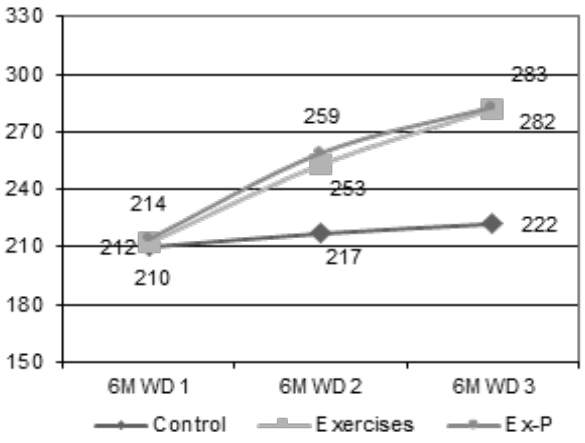

Fig. 2 – 6MWD-Females.

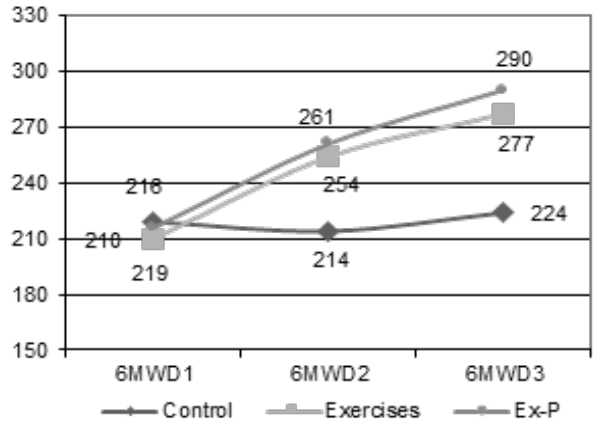

Fig. 3 – 6MWD-Males.

For the walking distance, we found that the evolution of values under physical treatment was much less influenced by smoking. Moreover, from the first determination of this parameter the values were about the same, and although they increased significantly at 12 and 24 weeks as can be seen in the following chart, the differences between smokers and non-smokers were statistically insignificant (Figs. 4 and 5).

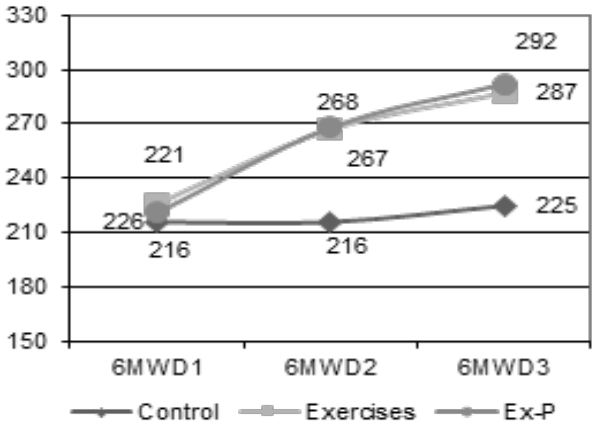

Fig. 4 – Non-smokers.

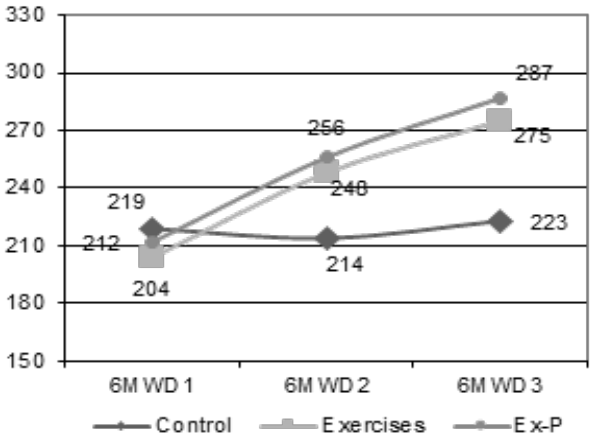

Fig. 5 – Smokers.

An interesting fact found in connection with the walking distance is its correlation with patients' age (Table III). Thus, a high correlation was noted for all three groups ever since the enrolment in the study, a correlation that increased more at the end of the 24 weeks for patients in groups 2 and 3 compared to those in the control group.

Table III
Age correlation.

Group	R	R Square	Adjusted R Square	Std. Error of the Estimate
Control	0.943[a]	0.888	0.886	6.469
Exercises	0.956[a]	0.913	0.909	3.499
Exercises Procedures	0.967[a]	0.935	0.933	3.739

a. Predictors: (Constant), age
Dependent Variable: 6MWD3

In patients with PAD, the same relationship between age and the ability to walk as that generally found in the population after a certain age was detected.

Discussions

In the presence of an atherothrombotic disease in one vascular bed (e.g., PAD), patients are at high risk of cardiovascular morbidity and mortality in other vascular beds (Cho et al., 2015; Steg et al., 2007). Regardless of the type, diabetes mellitus is associated with an increased risk of peripheral atherosclerosis. A systematic review of risk factors for PAD from 34 trials conducted since 1997 estimated the pooled relative risk of PAD due to diabetes mellitus with an odds ratio of 1.88 (95% CI: 1.66–2.14) (Fowkes et al., 2013). Diabetes increases the probability of distal disease in PAD and coronary artery disease (CAD), multi-vessel disease, which more frequently results in the need for coronary and/or peripheral bypass surgery compared to patients without diabetes (Ryden et al., 2014). Smoking is at present the most important risk factor for PAD. The corresponding amount of exposure (number of pack years) is associated with the severity of PAD, a higher amputation rate, peripheral prosthetic bypass occlusion and mortality (Willigendael et al., 2004).

The results obtained in our clinical study from the statistical analysis of the parameters were compared with the results of literature studies.

In a very recent clinical study from 2020, the outcome of multimodal supervised exercise training on walking performances and different hemodynamic parameters was evaluated in eighty-five patients with symptomatic lower extremity peripheral artery disease. Following a 3-month exercise program, 6MWD significantly increased (+14%; $P \leq .001$) (Calanca et al., 2020).

Recently, evidence has suggested that heated-water exercise therapy (HWET) is an effective intervention for PAD. PAD patients (n = 53) were recruited and randomly assigned to a land-based exercise training (LBET) group (n = 25) which performed treadmill walking, or a HWET group (n = 28) which performed walking in heated water for 12 weeks. Both groups had significantly increased 6MWD ($P < 0.05$) (Park et al., 2020).

In 2019, the American Journal of Physiology published the results of a 12-week randomized controlled trial of heat therapy vs. supervised exercise therapy for peripheral arterial disease. Following the interventions, the total walking distance during the 6-min walk test increased (from 350 m) by 41 m (95% CI: [13, 69], P = 0.006) regardless of the group, and the pain-free walking distance increased (from 170 m) by 43 m ([22, 63], P < 0.001) (Akerman et al., 2019).

A systematic review and meta-analysis including randomized controlled trials of exercise training versus usual medical care in persons with PAD concluded that exercise training produced significant 6-minute walk initial claudication improvements with mean difference (MD) 52.7 m (95% CI 24.7-80.6 m; p = 0.0002); total walking distance MD 34.9 m (95% CI 25.6-44.1 m; p < 0.00001) (Parmenter et al., 2015).

Conclusions

1. Physical exercise therapy is an important landmark in the medical treatment of intermittent claudication, through the regularity and not the intensity of exercises, a better use of energy resources in the muscles of the lower limbs, and it is a factor that contributes to slowing the evolution of claudication by increasing walking distance.

2. The beneficial effects of exercise and physical procedures on locomotion can be explained by various mechanisms, with improvements in gait economy and calf muscle perfusion being two of the mechanisms that act synergistically to improve claudication, decreasing metabolic demands and increasing oxygen supply.

3. All patients with PAD and intermittent claudication, who can perform an exercise program in complete clinical, cardiorespiratory and orthopedic conditions should be considered candidates for recovery with kinetic and physical means.

4. There were no complications during the physical therapy sessions or procedures and no complications in the control group, which could have been a consequence of enrolment in this study.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

All authors had an equal contribution to the manuscript.

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