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The effect of treadmill training on endothelial function and walking abilities in patients with peripheral arterial disease

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ABSTRACT

Background: In this prospective study we evaluated the effects of treadmill training on patients' walking ability, as well as endothelial function, high-sensitivity C-reactive protein (hs-CRP), and fibrinogen concentration.
Methods: A total of 67 patients with stable intermittent claudication were included in a 12-week supervised training program. An observational follow-up period then lasted a mean of 37 weeks. Forty patients completed follow-up. Changes in blood pressure, flow-mediated dilatation (FMD), and treadmill walking performance expressed as maximal walking time (MWT) were assessed before and after the training program and during the follow-up period. Moreover, ankle/brachial index (ABI), plasma levels of hs-CRP, fibrinogen, as well as a lipid profile were assessed before and after the training program.
Results: Maximal walking time improved significantly after treadmill training by 90% ($p < 0.001$) and after follow-up by 64% ($p < 0.001$) in comparison to baseline. FMD values increased by 43% ($p < 0.001$) after the training program, and by 29% ($p = 0.058$) after follow-up, compared to baseline. We noticed a significant decrease in hs-CRP concentration ($p = 0.025$) and an increase in ABI values ($p = 0.039$) in response to the treadmill training program. No effect on lipid profile was observed.
Conclusions: The 12-week treadmill training program prolonged the asymptomatic walking distance. The improvement in FMD indicates a systemic effect of the treadmill program on endothelial function. The supervised treadmill training provides an effective and safe treatment option in patients with PAD. The effects of unsupervised exercise during follow-up period after treadmill programs remain tentative and underestimated.

Introduction

Intermittent claudication

Intermittent claudication is the main symptom of peripheral arterial disease (PAD). It is usually defined as pain or muscle discomfort in the lower limb induced by exercise and relieved by rest [1]. The degree of atherosclerosis and its precise localization determine the character and severity of claudication. Patients with peripheral atherosclerosis, especially symptomatic patients with intermittent claudication demonstrate endothelial dysfunction [2].

Endothelial dysfunction

The endothelium plays a crucial role in vascular homeostasis, described as a balance between arterial diastole and systole. Endogenous NO is found to be the strongest vasodilator, and a crucial marker of endothelial function. Endothelial dysfunction is associated with decreased NO bioavailability, and the subsequent inability to induce vasodilation [3]. In effect the endothelium may express pro-inflammatory and pro-thrombotic features, activate oxidative reactions, and stimulate a proliferative state [4].

Most atherosclerosis risk factors such as hypertension, dyslipidemia, diabetes, smoking, obesity, or aging contribute to endothelial dysfunction. However, the pathogenesis of endothelial dysfunction is complex. The main cellular mechanism leading to this impairment is oxidative stress, which contributes to a decrease in flow-mediated dilatation (FMD) values in patients with PAD [5]. The oxidative modification of low-density lipoproteins (LDL) to ox-LDL (oxygenated low-density lipoproteins) is an important

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step in the endothelial pathogenesis linked to the development of atherosclerosis. Moreover, LDL and ox-LDL inhibit endothelial NO synthase (eNOS) activity [6]. Significant endothelial dysfunction, often many years worth, must take place before any symptoms or clinical complications arise [7]. Endothelial dysfunction is typically present from the earliest stages of atherosclerotic plaque development and could be, at least partly reversible at any time. The function and general health of the endothelium is influenced by various factors such as medications, diet, and physical activity [8,9]. As a measure of endothelial function the FMD value could be used to differentiate between patients more and less susceptible to the development and progression of atherosclerotic plaques, despite medical intervention. According to our knowledge, this is the first study with follow-up period after exercise training program, and FMD assessment.

Inflammation

The inflammatory process plays a key role in the pathogenesis of endothelial dysfunction. High sensitivity C-reactive protein (hs-CRP) is the principal marker of a pro-inflammatory state. The increased serum concentration of CRP in patients with atherosclerosis as such reflects the significance of the role of inflammation in the development of plaques [10]. CRP is mostly produced by liver, but also by vascular smooth muscle cells and epithelial cells [11].

Ridker et al. proved that elevated CRP in apparently healthy men predicts the future risk of symptomatic PAD development [12]. Several studies indicate that increased hs-CRP concentration in healthy people increases the risk of cardiovascular events and overall mortality rate by 1.5–2% [13]. According to the American Heart Association, hs-CRP concentrations are currently used in clinical practice to classify mild (<1 mg/l), moderate (1–3 mg/l), and severe (>3 mg/l) risk of cardiovascular events [14].

Treadmill training

Supervised walking programs are considered to be the most effective option to improve asymptomatic walking distance in patients with claudication [15]. The Intersociety Consensus for the Management of PAD (TASC II) states that the optimal intensity of exercise is that, which is sufficient to reproduce claudication pain considered to be moderate [1]. The safest and most effective training option in symptomatic PAD patients appears to be pain-free treadmill training interrupted at the onset of moderate pain [16]. According to our knowledge, the long-term effects of exercise on walking capacity have not been reported widely. This study aims to estimate the short- and long-term effects of treadmill training on endothelial function and walking capacity in patients with PAD.

Methods

Study population

Patients with symptomatic PAD (*i.e.* intermittent claudication) aged 48–80 years, all in Fontaine stage 2 were recruited from the angiology outpatient clinic. The diagnosis of PAD was confirmed by Doppler ultrasound or arteriography and an ankle/brachial index (ABI) of less than 0.9 at rest. All patients had a stable asymptomatic walking distance and were able to achieve 150 m without pain. The claudication distance was fixed by minimum six months preceding enrollment in the program. We excluded patients with a history of unstable angina, recent myocardial infarction, vascular surgery within the previous year, impaired cardiac or lung function, cancer, and kidney and liver disease. Furthermore, patients who were unable to walk on the treadmill at a speed of at least 3.2 km/h were also excluded. All patients had been treated pharmacologically with a stable regimen, which remained unchanged 6 months before enrollment, throughout the study and during follow-up. None of the participants were medicated with pentoxifylline, cilostazol, or selective cyclo-oxygenase-2 inhibitors. This study complies with the Declaration of Helsinki. All subjects provided written and informed consent before the investigation began. Study protocol was approved by the local ethical committee.

Study design

All patients were evaluated at baseline, after 12 weeks of supervised treadmill training, and after a mean follow-up period of 37 weeks by qualified medical staff.

During each evaluation period we measured maximal walking time (MWT) during a treadmill test, endothelial function, blood pressure, and smoking status. Neither the supervised, nor the unsupervised exercise program was performed during follow-up period. Patients underwent regular physical activity. Additionally ABI and blood analysis was performed before and after the treadmill program.

Exercise training

The exercise program consisted of 12 weeks of supervised, intermittent treadmill walking. Exercise sessions were conducted three times a week. During each exercise session, treadmill walking was at speed of 3.2 km/h and the grade individually determined for each patient that would induce claudication within 3–5 min [1]. The exercise was interrupted when the patient stopped at the onset of claudication. The severity of claudication pain experienced by the patient was determined on a scale, where 1 = no pain, 2 = onset of claudication, 3 = mild pain, 4 = moderate pain, and 5 = maximal pain [17]. After exercise, the patient rested until claudication had abated and then walking was resumed. This cycle of intermittent walking exercise was applied for 35 min at the start of the program with progressive increase of session time by 5 min per 2 weeks. At subsequent visits, the grade of the treadmill was increased, if the patient was able to walk for 8 min or longer at the previous workload [9].

Treadmill testing

Walking abilities (MWT) were assessed during morning hours according to the graded treadmill protocol [18]. Subjects walked on the treadmill (Gait Trainer, Biodex, Shirley, NY, USA) at an initial workload of 3.2 km/h, 0% grade for 2 min. Subsequent stages increased 2% in grade every 2 min. The speed was set constant (3.2 km/h) throughout the test. The MWT was recorded when the patient refused to continue the test because of severe claudication pain (level 5 on pain scale) [17]. Patients were instructed not to use handrail support during the treadmill test. The treadmill was calibrated prior to each testing. The test was repeated on the next day and the best of two measurements were used in data analysis.

Endothelial function assessment

The FMD of the brachial artery was assessed using a high resolution echo-Doppler ultrasound (Sequoia 512, Acuson, linear probe 7 MHz; Siemens, Erlangen, Germany). The examination was performed in a quiet, temperature-controlled room (23,0–24,0 °C) after a 15-min resting period. The subjects reported to the laboratory between 07.00 and 08.00 h after overnight fasting. Patients were instructed to refrain from physical exercises, caffeine beverages, and tobacco use for 12 h prior the test. All temporary medications were withheld for 24 h before testing. The subject was

positioned supine with the arm fixed in a comfortable position for imaging the brachial artery 2 cm above the antecubital fossa in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for imaging [19]. The images were recorded for 30 s at rest. Thereafter, arterial occlusion was produced with the pneumatic sphygmomanometric cuff placed below the antecubital fossa and inflated 50 mmHg over the systolic blood pressure. After 5 min of ischemia, the cuff was deflated. The diameter of the brachial artery was measured for 60–90 s after deflation. The mean of 3 maximal end-diastolic diameter measurements was assumed to calculate FMD value. The percent change in artery diameter during post-occlusive reactive hyperemia was taken as the value of FMD [20]. The measurement was performed at rest and repeated 15 min after the treadmill test to maximal claudication pain. The measurement was made by blinded, trained, and experienced medical staff.

Biochemical analyses

Blood samples were collected the day following a training session after an overnight fast. Patients were asked to refrain from smoking 12 h prior to the blood test. Blood samples for the analysis of fibrinogen, high-sensitivity C-reactive protein (hs-CRP) and lipid profile: total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides, were drawn from the forearm vein (between 09.00 h and 10.00 h) after 30 min rest and immediately sent to the laboratory.

Other measures

To calculate the ABI, we measured blood pressure in the upper and lower limbs. We used continuous wave Doppler detector in the case of the lower limbs, and for the upper limbs regular sphygmomanometer. Measurements were performed on the brachial artery in the upper limbs and the posterior tibial and dorsalis pedis artery in the lower limbs. In the case of different pressures in the same limb we took into account the higher value. ABI was calculated as the ratio of systolic blood pressure in the foot to systolic blood pressure in the arm [1]. Smoking status was determined as the average number of cigarettes smoked daily and the number of years smoked, height and weight were measured before and after the program, and body mass index (BMI) was calculated.

Statistical analysis

Changes in variables over 12 weeks of the training program and the follow-up period were analyzed by Wilcoxon signed-rank test and ANOVA. The Spearman rank correlation coefficients were used to assess the possible relationship between variables. The statistical analyses were performed using Statistica 10.0 software (http://statistica.software.informer.com/10.0/). The data are expressed as means, SD, medians, and interquartile range (IQR) when appropriate. Statistical significance was accepted at a 0.05 level of probability.

Results

From among 85 enlisted participants, 67 completed the 12-week training program. The mean duration of follow-up was 37 weeks (min. 16 weeks, max. 54 weeks). Of the 67 patients who completed training, 27 were lost to follow-up (18 lack of desire to continue the research, 2 urgent abdominal surgery, 1 coronary artery disease exacerbation, 2 arrhythmias, 2 orthopedic diseases, 1 obstructive pulmonary disease exacerbation, 1 urgent deterioration of PAD symptoms and following angioplasty), and 40 completed the entire study. The clinical characteristics of the 67 patients who completed the 12-week program is presented in Table 1. The distribution of culprit lesions of lower limb arteries is presented in Table 2.

After the exercise program we observed an insignificant increase in LDL, HDL, TG, and total cholesterol, whereas serum fibrinogen slightly decreased (4.39 ± 1.52 g/l *vs.* 4.28 ± 1.18 g/l, $p = 0.33$). We observed a drop in hs-CRP concentration (3.33 ± 4.07 mg/l *vs.* 2.54 ± 2.51 mg/l, $p = 0.025$) and an increase in ABI (0.63 ± 0.17 *vs.* 0.66 ± 0.18, $p = 0.039$) (Table 3). However, after follow-up ABI value decreased significantly compared to that after exercise program (0.66 ± 0.18 *vs.* 0.65 ± 0.16, $p = 0.015$), and became insignificantly higher compared to entry value ($p = 0.89$). After 12 weeks, the exercise program resulted in a significant rise in pre-exercise FMD ($4.34 \pm 2.37\%$ *vs.* $6.15 \pm 2.4\%$, $p < 0.001$) as well as post-exercise FMD ($4.38 \pm 2.29\%$ *vs.* $6.26 \pm 2.62\%$, $p < 0.001$). After follow-up the pre-exercise ($4.34 \pm 2.37\%$ *vs.* $4.74 \pm 2.66\%$,

Table 1
Baseline group characteristics.

	Overall group ($n = 67$)
Male:female	41:26
Age (years)	65.5 ± 7.7
Smoking, *n* (%)	36 (53.73)
Smoking (years)	34.33 ± 12.63
Cigarettes/day	21 ± 11.2
Peripheral artery disease	
Claudication (years)	8.99 ± 6.47
Previous endovascular intervention of peripheral arteries, *n* (%)	19 (28.35)
Previous bypass grafting surgery, *n* (%)	4 (5.97)
Associated diseases, *n* (%)	
Coronary artery disease	22 (32.83)
Previous myocardial infarction	3 (4.47)
Previous endovascular intervention of coronary arteries	3 (4.47)
Previous coronary artery bypass grafting surgery	2 (2.98)
Hypertension, *n* (%)	55 (82.08)
Diabetes, *n* (%)	14 (20.89)
Chronic obstructive pulmonary disease/bronchial asthma	7 (10.44)
Treatment, *n* (%)	
Aspirin	64 (95.52)
Clopidogrel/ticlopidine	12 (17.91)
Statins/fibrates/ezetimibe	67 (100)
Angiotensin-converting enzyme inhibitors/aldosterone receptors blockers	39 (58.2)
Calcium channel blockers	22 (32.83)
Beta-blockers	34 (50.74)
Diuretics	19 (28.35)

Values are mean ± SD and percentages (in parentheses) when appropriate.

Table 2
Location of the lower limb artery lesions in patients who completed the training program.

The types of lesion, *n* (%)	Location	Cases, *n* (%)
Total, 67 (100)	Crural artery	33 (49.25)
	Popliteal artery	16 (23.88)
	Femoral artery	43 (64.17)
	Iliac artery	7 (10.44)
Single segmental, 21 (31.34)	Crural artery	4 (19.04)
	Popliteal artery	3 (14.28)
	Femoral artery	12 (57.14)
	Iliac artery	2 (9.52)
Two segmental, 29 (43.28)	Popliteal–crural artery	4 (13.79)
	Femoral–crural artery	19 (65.51)
	Femoral–popliteal artery	1 (3.44)
	Iliac–femoral artery	5 (17.24)
Three or more segments, 6 (8.95)	Femoral–popliteal–crural artery	4 (66.67)
	Iliac–femoral–crural artery	1 (16.67)
	Iliac–femoral–popliteal artery	0 (0)
	Iliac–femoral–popliteal–crural artery	1 (16.67)

Table 3
Changes in biochemical variables, BMI, and ABI after training program.

Variables	Baseline	Week 12	*p*
Total-cholesterol (mmol/l)	4.65 ± 1.08 4.4 [3.9–5.3]	4.74 ± 1.07 4.6 [4.0–5.3]	0.45
LDL-cholesterol (mmol/l)	2.49 ± 1.05 2.29 [1.75–3.06]	2.52 ± 1.05 2.32 [1.9–2.91]	0.98
HDL-cholesterol (mmol/l)	1.35 ± 0.29 1.35 [1.1–1.5]	1.36 ± 0.27 1.3 [1.2–1.5]	0.47
Triglycerides (mmol/l)	1.77 ± 0.98 1.42 [1.1–2.18]	1.88 ± 1.13 1.62 [1.14–2.24]	0.39
hs-CRP (mg/l)	3.33 ± 4.07 2.225 [1.08–3.87]	2.54 ± 2.51 1.46 [0.79–3.3]	0.025
Fibrinogen (g/l)	4.39 ± 1.52 4.25 [3.4–5.22]	4.28 ± 1.18 4.2 [3.4–5.0]	0.33
BMI (kg/m^2)	26.3 ± 3.6 26.32 [23.74–28.32]	25.97 ± 3.42 25.76 [23.8–27.72]	0.38
ABI	0.63 ± 0.17 0.66 [0.5–0.76]	0.66 ± 0.18 0.675 [0.52–0.79]	0.039

Mean value ± standard deviation; median [lower–upper quartile]; the Wilcoxon signed-rank test; ABI, ankle/brachial index; BMI, body mass index; hs-CRP, high sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

$p = 0.74$) and post-exercise (4.38 ± 2.29% to 5.68 ± 3.02%, $p = 0.058$) FMD declined and remained elevated compared to baseline, albeit insignificantly. The drop of pre- and post-exercise FMD values after follow-up period, in comparison to measurements performed after exercise program was not significant ($p = 0.13$, $p = 0.49$). There was no statistically significant difference between pre- and post-exercise FMD, however post-exercise values were consistently higher, especially at the end of follow-up ($p = 0.09$) (Fig. 1). The baseline brachial artery diameter did not differ significantly between pre- and post-exercise measurement at each time point (4.44 ± 0.65 mm *vs.* 4.38 ± 0.63 mm, $p = 0.31$; 4.42 ± 0.58 mm *vs.* 4.42 ± 0.55 mm, $p = 0.99$; 4.6 ± 0.61 mm *vs.* 4.6 ± 0.63 mm, $p = 0.91$). There was also no significant difference in baseline brachial artery diameter between following time points in pre- and post-exercise values. In the clinical picture, a significant improvement in exercise tolerance, assessed by the maximal walking time (MWT) was observed after training (470.81 ± 187.11 s *vs.* 898 ± 358.72 s, $p < 0.001$). Likewise, after follow-up the MWT decreased significantly ($p < 0.001$, in comparison to measurements made after exercise program); however, maintained a significant improvement in comparison to baseline (470.81 ± 187.11 s *vs.* 775.36 ± 345.37 s, $p < 0.001$) (Fig. 2). Neither the smoking status nor the BMI changed significantly ($p > 0.05$).

No significant correlation between the FMD, MWT (Figs. 3 and 4), BMI, ABI, biochemical measurements, smoking status, duration of PAD, and/or age was noticed at baseline, after exercise program, and follow-up period. Interestingly, even the improvement in FMD (ΔFMD) after 12 weeks of exercise program and follow-up period did not correlate with improvement of MWT (ΔMWT) and BMI value (ΔABI), respectively. We noticed a negative correlation between the extent of improvement of FMD and smoking quantity (pack years) ($p < 0.05$).

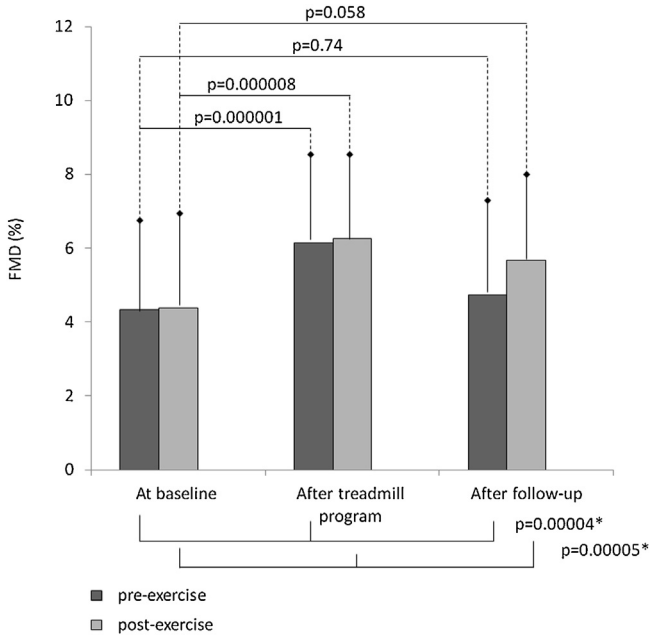

Fig. 1. The maximal walking time at baseline, after 12 weeks of the treadmill training and after follow-up period. The Wilcoxon signed-rank test, *ANOVA. FMD, flow-mediated dilatation.

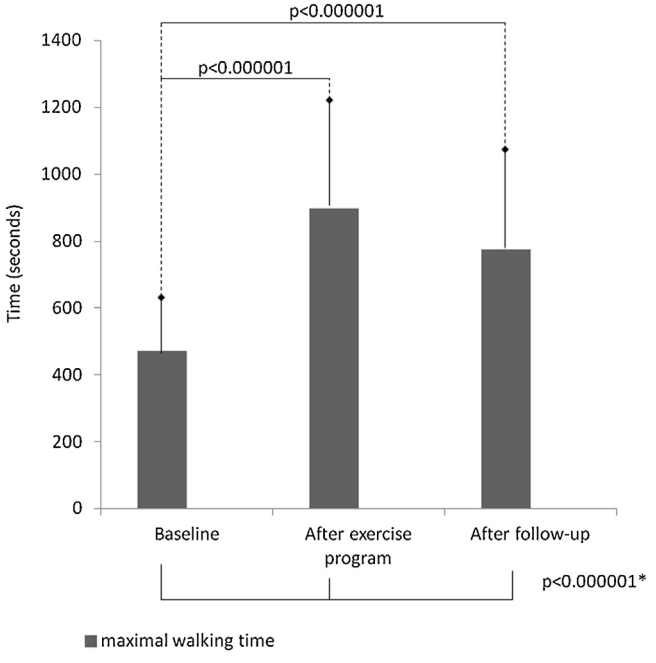

Fig. 2. The rest and post-exercise flow-mediated dilatation values at baseline, after 12 weeks of the treadmill training and after follow-up period. The Wilcoxon signed-rank test, *ANOVA.

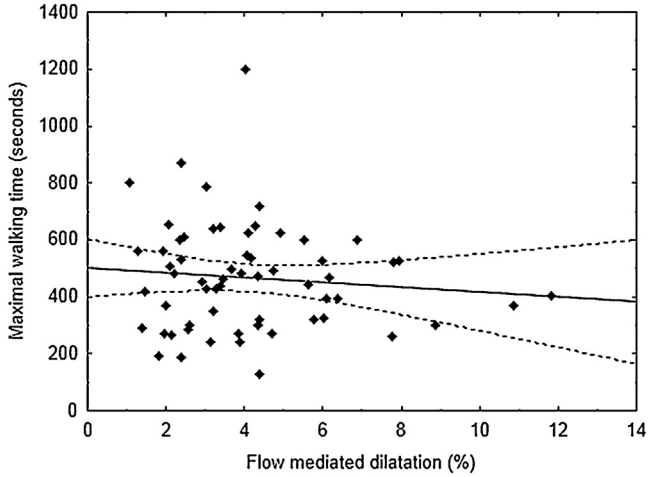

Fig. 3. Correlation between flow-mediated dilatation and maximal walking time before exercise program ($r = -0.1$, $p = 0.43$, CI = 95%).

Discussion

Walking abilities

This supervised exercise program proved efficacious in enhancing the patients' exercise tolerance. We observed a significant improvement in MWT after training and follow-up in comparison to baseline. This improvement in walking abilities was comparable to that reported in so far published studies [19]. However, publications with long-term observations and follow-up of walking ability are limited. Keo et al. noticed a significant improvement of maximal walking distance (MWD) after a 12-week training program in patients with PAD, which persisted as a significant clinical improvement for 39 months of follow-up [21]. Moreover, Perkins et al. demonstrated that the long-term impact of treadmill training on MWD in patients with PAD is comparable to percutaneous transluminal angioplasty (PTA) after approximately 6 years of follow-up. The effectiveness of supervised treadmill training depended mostly on the location of the occluded artery [22]. However, in our study, the population was not evaluated in this respect. Undoubtedly, intensity and type of physical activity during follow-up period plays a crucial role in sustaining MWT. It is difficult to assess accurately the extent of home exercise and differentiate it objectively between patients. The impact of unsupervised exercise programs on walking abilities during follow-up period has not been clearly defined so far. Additionally, we lost 27 of 67 patients (40%), during the follow-up period which could influence final results, despite the fact that most of the patients refused follow-up visit most likely due to lack of further benefit.

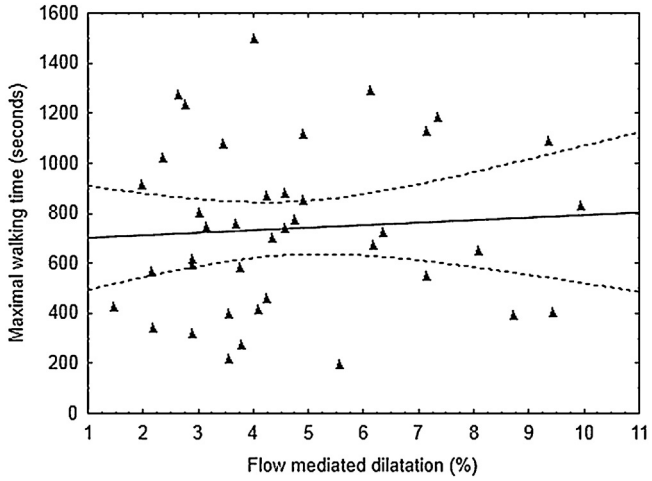

Fig. 4. Correlation between flow-mediated dilatation and maximal walking time after follow-up period ($r = 0.07$, $p = 0.66$, CI = 95%).

As in our findings, non-smokers seemed to benefit more than smokers from an exercise regimen [21]. Similar results were obtained by Rossini et al. after 4 weeks of supervised training and one year follow-up in patients with moderate-to-severe claudication [23]. We did not observe a significant difference in MWT and FMD after the training program in comparison to follow-up between smokers and non-smokers, however the lack of sustained benefits to MWT at follow-up was slightly, although not significantly smaller in non-smokers than in smokers.

Endothelial function

Interestingly, although not surprisingly, we observed a significant improvement in FMD after a treadmill training program. At follow-up, the improvement in FMD values was maintained, although without statistical significance. Impaired endothelial function, associated with high levels of CRP and fibrinogen, has been demonstrated in patients with PAD [23]. Possible acute endothelial injury, induced by repeated training sessions did not influence significant change in pre- and post-exercise FMD at each time point. Preliminary studies suggest that restoration of normal endothelial function is coupled with a reduction in cardiovascular events, as well as the improvement in walking abilities in patients with claudication [2]. Although the beneficial effects of exercise training on endothelial function have been reported previously, the impact of exercise during follow-up period is still insufficiently investigated [24]. It was postulated, that systemic effects of physical activity may have an impact on endothelial function [25]. The mechanism of such an improvement was generally attributed to the enhanced endothelial synthesis of NO, which is stimulated by an increase in blood flow [26]. Improvement in blood flow could be due to collateralization, which has been suggested in patients with coronary artery disease after exercise training [27]. Confirmation of this thesis is justified by a significant improvement in ABI at the end of the program, which is closely associated with an increase in blood flow. However, after the training program and follow-up, we did not observe correlation between the change in FMD and ABI. Another mechanism explaining an improvement in endothelial function could be associated with altered lipoprotein levels [28]. Albeit, we did not observe significant changes in lipid profile in our study, with increased tendency. This could be explained by a relatively small effect of physical activity on lipid profile in comparison to statin therapy and a short period of study. The positive systemic effects of exercise on endothelial function, could be partly explained by a decline in the inflammatory response (represented by a decrease in pro-inflammatory markers hs-CRP, *etc.*), which was observed in our research. Additionally, risk factors such as gender, obesity, concomitant diseases could modify the effect of physical activity on FMD. The improvement in endothelial function after exercise training with tendency to be maintained at a high level during follow-up period in comparison to baseline values, could suggest that the endothelial changes induced during the 12-week exercise training, altered its function for almost 10 months on average, even after the cessation of physical activity. It is difficult to compare our results to other studies, because there is limited research done in this area, particularly those with FMD measurement during follow-up. We explain this by speculating that exercise may induce a change in the genetic expression and hence production of particular proteins involved with the improvement in endothelial function, on a translational and transcriptional level which is maintained for months.

Inflammation

Treadmill training is both a safe and cheap therapeutic approach and importantly in further observation does not escalate the inflammatory process in patients with claudication [29]. Elevated levels of CRP and fibrinogen, initially observed prior to commencing training, significantly declined after 3 months, yet only CRP remained significantly lower at follow-up. This may prove to be enough though, as CRP is an important prognostic indicator of future cardiovascular events in persons both with and without atherosclerosis [14]. According to the American Heart Association guidelines, a decline in mean CRP concentration reduces the overall risk of cardiovascular disease from high to moderate [14].

Andreozzi et al. suggested that moderate hemodynamic stress reduces the level of pro-inflammatory markers and improves FMD through ischemic preconditioning [20]. Based on our findings, an increase in FMD after treadmill training was accompanied by a decrease in hs-CRP. These parameters, taken as intriguing yet sensible representations of endothelial function and endothelial inflammation could, at least in part, explain the systemic effects of treadmill training as a reduction in the inflammatory response leading to an appropriate improvement in endothelial function. On the contrary, Saxton et al. reported only a tendency, without statistical significance for 24 weeks of upper and lower limb exercise to reduce hs-CRP [30]. The influence of exercise training on fibrinogen in patients with claudication is not clear. Some scientists observed significant rise in fibrinogen level after physical training, whereas others did not [31,32]. The decline in pro-inflammatory markers did not correlate well with changes in lipid profile. Our results as well as those of previous studies indicate that exercise tends to decrease rather than increase the pro-inflammatory markers [19].

Study limitations

The limitation of our study is the lack of a 'no-training' control group and a 'healthy' training control group, as well as the potential confounding variables of patient medication usage or the endothelium's adaptation tolerance to exercise. We could not control total daily physical activity, which to begin with is quite limited in this patient subset and undoubtedly differed between all participants. These could have had a positively and negatively distorting impact on the final results.

Conclusions

In conclusion, based on the improvement in both endothelial function and walking tolerance after a training program, the efficacy of supervised exercise training seems to be irrefutable. The decline in pro-inflammatory markers reduced the risk of future cardiovascular events. A 12-week training program induces permanent changes in the peripheral vascularization, and improvement in FMD and walking indices, even after cessation of supervised and regular exercise. We also conclude that lipid profile is not affected by supervised and repetitive exercise. The effect of an unsupervised exercise program, particularly after a supervised exercise program needs to be further diagnosed and observed.

Conflict of interest

All authors have no conflict of interest to declare.

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