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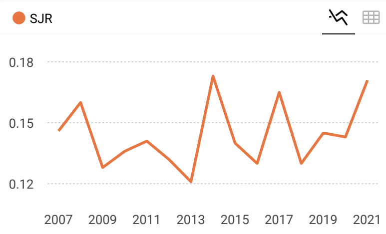

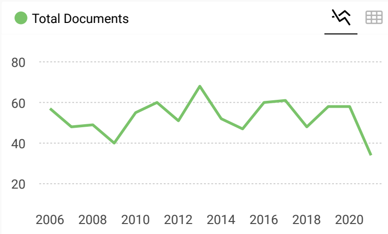

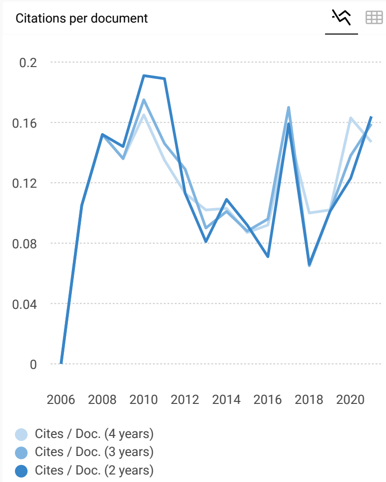

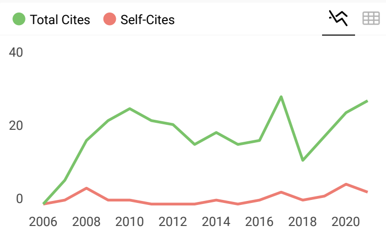

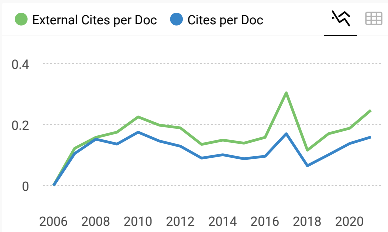

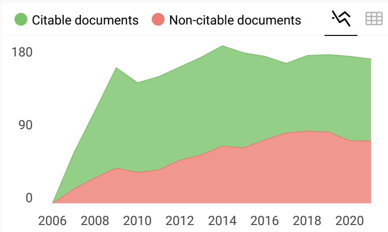

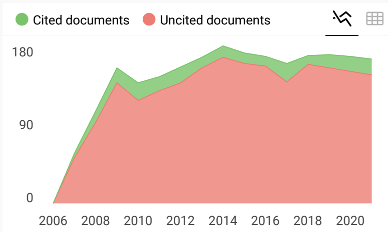

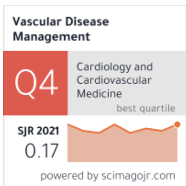

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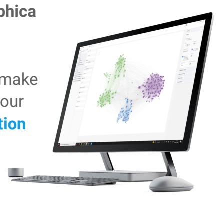

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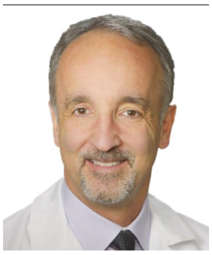

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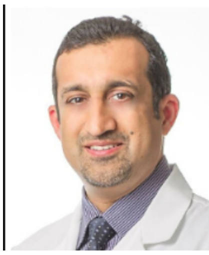

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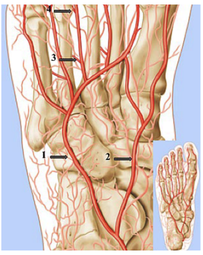

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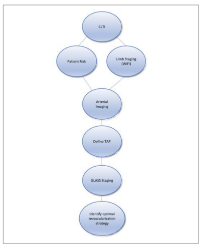

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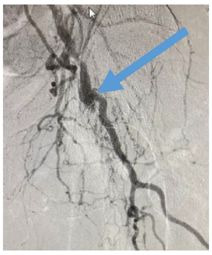

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1. Basic characteristics of subjects

Parameter	Category	Value (mea
rs		57.84 ±
	Male	11 (57.
scular risk factor	Diabetes mellitus	16 (84.
	Hypertension	14 (73.
	Dyslipidemia	16 (84.
	Smoking	6 (31.6
	Obese (BMI > 30)	4 (21.1
ation	Left side only	9 (47.4
	Right side only	6 (31.6
	Left and right sides	4 (21.1

tions: BMI, body mass index; PAD, peripheral artery disease; dard deviation

Effect of Home-Based Exercise Training on Plasma Vascular Endothelial Growth Factor and Ankle-Brachial Index in Patients With Mild Peripheral Artery Disease: A Pilot Study

Column

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Effect of Home-Based Exercise Training on Plasma Vascular Endothelial Growth Factor and Ankle-Brachial Index in Patients With Mild Peripheral Artery Disease: A Pilot Study

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Abstract. Background: Peripheral artery disease (PAD) is a manifestation of atherosclerosis in the peripheral arteries of the inferior extremities, and is associated with high morbidity and mortality rates. Increased levels of vascular endothelial growth factor (VEGF) can stimulate the process of angiogenesis and collateral artery formation in patients with PAD. Production of VEGF can be improved with regular exercise training. Home-based training offers more convenience in terms of time and place than does standard exercise training.
Objective: The study aims to clarify the effect of home-based exercise training on VEGF level and ankle-brachial index (ABI) in patients with PAD.
Methods: In a quasi-experimental study, 19 patients with PAD underwent home-based exercise training for 8 weeks. VEGF levels were measured and ABI was evaluated before and after 8 weeks of home-based exercise training. Before exercise training, 10 patients had an ABI of 0.9 or less in the right limb, and 13 had an ABI of 0.9 or lower in the left limb.
Results: The results showed that both ABIs significantly increased after home-based exercise training (right ABI: mean difference = 0.11; 95% confidence interval [CI], 0.06–0.16; *P*=0.001; left ABI: mean difference = 0.12; 95% CI, 0.09–0.16; *P*=0.000). The levels of VEGF before and after home-based exercise training VEGF level were significantly different (*P*=0.0001)
Conclusion: Home-based exercise training improved VEGF level and ABI in patients with PAD.

VASCULAR DISEASE MANAGEMENT 2019;16(12):Exxx-Exxx.
Key words: Peripheral artery disease, atherosclerosis, vascular endothelial growth factor, ankle-brachial index, home-based exercise training, exercise, angiogenesis

Peripheral artery disease (PAD) is characterized by inadequate blood flow to the peripheral circulation due to plaque accumulation on the artery walls, resulting in intermittent claudication.[1] Approximately 8 million Americans currently have a diagnosis of PAD.[2] Surgical or nonsurgical methods may be applied to prevent disease progression, improve functional performance, and reduce intermittent claudication in patients with PAD.

Over the past decade, several trials have been conducted to stimulate the neovascularization process, with the goal of restoring post-ischemic muscle perfusion in patients with PAD.[3] One topic of interest has been vascular endothelial growth factor A (VEGF-A, or simply VEGF). VEGF is a key promoter of angiogenesis and the major target of proangiogenic therapy for PAD. Plasma VEGF increases the proliferation and migration of endothelial cells.[4] Studies have shown that exercise training increases VEGF level, so exercise training may be promising as a proangiogenic therapy with a low potential for harmful side effects.[5] Our study attempted to better understand the effects of home-based exercise training on VEGF level and ankle-brachial index (ABI) in patients with PAD.

METHODS

A quasi-experimental study was conducted at the Vascular Clinic of Dr Soetomo General Hospital, Surabaya, Indonesia. Patients with PAD and an ABI of 0.9 or lower were enrolled in the study during March and April 2018. PAD was diagnosed based on the presence of either classical or atypical intermittent claudication, physical examination, and ABI. Patients who could not walk alone or with assistance, had undergone revascularization therapy for PAD, had neuromuscular comorbidities, and who had unestablished cardiorespiratory status were excluded. Informed consent was obtained from each participant. Ethical clearance was approved by the Ethical Committee of Airlangga University and Dr Soetomo General

Table 1. Basic characteristics of subjects

Parameter	Category	Value (mean ± SD)
Age, years		57.84 ± 8.04
Sex	Male	11 (57.9%)
Cardiovascular risk factor	Diabetes mellitus	16 (84.2%)
	Hypertension	14 (73.7%)
	Dyslipidemia	16 (84.2%)
	Smoking	6 (31.6%)
	Obese (BMI > 30)	4 (21.1%)
PAD location	Left side only	9 (47.4%)
	Right side only	6 (31.6%)
	Left and right sides	4 (21.1%)

Abbreviations: BMI, body mass index; PAD, peripheral artery disease; SD, standard deviation

Table 2. VEGF level before and after exercise training

VEGF	N	Mean ± SD	Median (IQR)	*P*
Before exercise	19	414.84 ± 211.181	377 (266–492)	
After exercise	19	507.89 ± 221.826	431 (343–646)	P = 0.0001

Abbreviations: IQR, interquartile range; SD, standard deviation; VEGF, vascular endothelial growth factor A.

Table 3. ABI before and after home-based exercise training in a patient with PAD in the right and left lower extremities

Group	N	Mean ± SD before exercise	Mean ± SD after exercise	Mean difference (95% CI)	*P*
Right ABI	10	0.85 ± 0.05	0.96 ± 0.09	0.11 (0.06–0.16)	0.001
Left ABI	13	0.86 ± 0.05	0.98 ± 0.05	0.12 (0.09–0.16)	0.000

Abbreviations: ABI, ankle-brachial index; CI, confidence interval; PAD, peripheral artery disease; SD, standard deviation.

Hospital (Ethical Clearance Number 587/Panke.KKE/X/2017).

All participants were educated on the basic management of medical emergencies at home. VEGF level and ABIs were measured before home-based exercise training. ABIs were evaluated with a VaSera VS 1500 Vascular Screening System (Fukuda Denshi, Tokyo) by a blinded technician. ABI, which was calculated for each leg, was determined by taking the higher value of the systolic blood pressure of the pedis or posterior tibial artery (not the average of systolic blood pressure of both arteries) and dividing it by the systolic blood pressure of the brachial artery. Measurements were performed twice, and the average of both measurements was considered. Serum was collected, and the sandwich enzyme-linked immunosorbent assay (ELISA) was used to assess VEGF levels.

Each participant took a 6-minute walking test, and findings were used to determine the exercise prescription and to adjust the periodic step setting of the metronome. Participants performed home-based exercises in accordance with the metronome rhythms every day for 8 weeks. At the end of the first, third, and sixth weeks, 6-minute walking tests were conducted again to evaluate and adjust the prescription. Each prescription was adjusted to achieve a maximal oxygen uptake reserve target of 40% to 50% after the first week, 50% to 60% after the third week, and greater than 60% after the sixth week. Each training session included 5 to 10 minutes of warming up, 30 minutes of walking exercise, and 5 to 10 minutes of cooling down. The exercise was supervised by medical professionals three times per week. After 8 weeks of training, VEGF levels and ABIs were measured again. Participants were asked to record and report any adverse event during the exercise in a logbook.

The data collected are expressed in percentages and mean ± standard deviations. The difference in ABI before and after exercise was analyzed with the paired t-test. The difference between preexercise and postexercise VEGF levels was analyzed with the Wilcoxon signed-rank test. All analyses were performed with the use of SPSS 24.0 software.

RESULTS

Of the original 32 patients screened for this study, 13 were excluded. The basic characteristics of the remaining 19 patients are summarized in **Table 1**. The mean age of the patients was 57.84 ± 8 years, and the majority were male. The major comorbid conditions were hypertension, diabetes mellitus, and dyslipidemia.

The average initial VEGF level was 414.84 ± 211.181 pg/mL (**Table 2**). VEGF levels after home-based exercise training were increased, at a mean of 507.89 ± 221.826 pg/mL. The difference between them was statistically significant (Z score=−3.823, *P*=0.0001).

Right ABI was 0.9 or lower in 10 patients before the exercise in this study. **Table 3** shows that ABI significantly increased in the right lower limb after completing exercise training (mean difference=0.11; 95% CI, 0.06–0.16; *P*=0.001). Left ABI was 0.9 or lower before exercise in 13 patients. After exercise training, the ABI in the left lower limb was significantly increased (mean difference=0.12; 95% CI, 0.09–0.16; *P*=0.000).

There were 4 samples with bilateral mild PAD, and the ABI and VEGF values before and after exercise are shown in **Table 4**. Patients with bilateral PAD had a lower ABI and higher VEGF value than those diagnosed with PAD in a single leg.

DISCUSSION

This study demonstrated that home-based exercise training for 8 weeks was associated with increased circulating VEGF levels in patients with PAD. Various researchers have reported contradictory results for circulating VEGF levels in response to physical exercise. Increases in the level of circulating VEGF after a short duration of exercise were reported by several investigators.[5,6] However, other studies have shown that exercise either has no effect or even demonstrates a decrease has no effect or even a decrease in VEGF level.[7-9]

Table 4. ABI and VEGF value before and after home-based exercise training in patients with bilateral and single PAD

Patient number	ABI L pre	ABI L post	ABI R pre	ABI R post	VEGF pre	VEGF post
1.	0.77	1.07	0.86	1.13	201	276
2.	0.90	1.00	0.76	0.82	510	566
3.	0.82	0.89	0.82	0.87	703	898
4.	0.82	0.94	0.80	0.93	444	526
Mean of those with bilateral PAD	0.85 ± 0.06	0.96 ± 0.11	0.81 ± 0.04	0.94 ± 0.14	464.5 ± 207.2	566.5 ± 255.6
Mean of those with single PAD	0.87 ± 0.05	0.99 ± 0.04	0.88 ± 0.03	0.98 ± 0.06	406.4 ± 224.8	507.5 ± 222.6

The differences in study results can be ascribed to several factors, such as differences in experimental protocols, and different intensity and duration of the exercise training. High-intensity training produced a significant increase in circulating VEGF levels, whereas low-intensity training did not.[10,11] However, other researchers have reported decreased circulating VEGF levels after high-intensity training.[12,13] Greater mechanical and metabolic stimuli during high-intensity interval training led to a greater release of VEGF from the muscle into the circulation. However, while high-intensity training is suitable for athletes and healthy people, it may not be suitable for patients with PAD whose physical fitness level is poor. In the majority of pertinent studies, the level of circulating VEGF was measured shortly after short-term exercise. Depending on the time of measurement, short-term exercise may not reflect the circulating VEGF levels because other muscle may uptake the VEGF released from skeletal muscle.[14] Prolonged exercise might induce a long-lasting increase in circulating VEGF.[15]

In ischemic musculoskeletal tissues of the lower limb, improved oxygenation during exercise training stimulates VEGF release.[16-18] An increase in VEGF expression in skeletal muscle is associated with a significant increase in the number of capillaries per muscle.[19,20] Increased capillary density may contribute to improvement in functional capacity in patients with PAD.[21]

In our study, we found that ABI improved in both left and right lower limbs after the exercise training in patients with PAD. This result was similar to that of previous studies in which ABI improved in diabetic patients with intermittent claudication after exercise.[22] However, according to one meta-analysis, exercise training did not improve ABI in several studies; the pooled effect was −0.01 (95% CI, −0.5–0.4).[23] The pooled mean baseline ABI was no more than 0.72, which was lower than the ABI in our study. Results of a recent systematic review were similar to those in the meta-analysis.[24] Results that conflict with those of our study may indicate that exercise training was more effective in increasing ABI when the ABI was already high than when the ABI was low.

ABI improvement indicated that distal blood flow through collateral vessels improved as a result of arteriogenesis. Arteriogenesis induced by exercise involves structural remodeling, beginning with phenotypic shift, migration, and proliferation of vascular smooth muscle cells, which leads to neointima formation and causes the vessel structure to become contractile.[25] Exercise also increases capillary density through the process of angiogenesis, and results in greater oxygenation.[26] Relatively low oxygen tension in active muscle is an important sign of angiogenesis as a result of the upregulation of VEGF.[27] Mechanical and metabolic stimuli such as adenosine also induce angiogenesis in active muscle during exercise.[28,29]

The 6-minute walking test was used in our study as a basis for devising the home-based exercise training. The 6-minute walking test is a validated measure of walking endurance in patients with PAD. Home-based exercise significantly improved the treadmill walking distance and physical activity performance of patients with PAD.[30,31] Therefore, we considered home-based exercise training as an alternative to the standard treadmill exercise.

The limitation of our study was that we did not group subjects by age and risk factors. Therefore, we were unable to analyze the effects of the exercise training on the basis of age and risk factors. The process of exercise-induced angiogenesis is complex, and so it may have been triggered by a mechanism other than VEGF.

CONCLUSION

Home-based exercise training in patients with PAD for 8 weeks increased plasma VEGF level and ABI. We believe that this training had a beneficial effect in patients with PAD. Our study supports the idea that exercise training to improve the condition of patients with PAD can be performed at home. ■

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no financial relationships or conflicts of interest regarding the content herein. Manuscript submitted June 17, 2019, manuscript accepted August 2, 2019.

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