Bicycle exercise training improves ambulation in patients with peripheral artery disease

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ABSTRACT

Objective: Exercise training has multiple beneficial effects in patients with arteriosclerotic diseases; however, the exact underlying mechanisms of the effects are not completely understood. This study aimed to evaluate the effectiveness of a supervised exercise program in improving gait parameters, including the variability and walking performance of lower limb movements, in patients with peripheral artery disease (PAD) and intermittent claudication (IC).

Methods: Sixteen patients with a history of PAD and IC were recruited for this study, and they completed a 3-month supervised bicycle exercise program. The ankle-brachial index and responses to quality of life (QOL) questionnaires were evaluated. Near-infrared spectroscopy was also performed to determine the hemoglobin oxygen saturation in the calf. Patients' kinematics and dynamics, including joint range of motion and muscle tension, were evaluated using an optical motion capture system. Computed tomography images of each muscle were assessed by manual outlining. Data were collected before and after the supervised bicycle exercise program, and differences were analyzed.

Results: Significant differences were not found in step length, ankle-brachial index, and hemoglobin oxygen saturation before and after the supervised bicycle exercise program; however, IC distance ($P = .034$), maximum walking distance ($P = .006$), and all QOL questionnaire scores ($P < .001$) showed significant improvement. Hip range of motion ($P = .035$), maximum hip joint torque (right, $P = .031$; left, $P = .044$), maximum tension of the gluteus maximus muscle (right, $P = .044$; left, $P = .042$), and maximum hip joint work (right, $P = .048$; left, $P = .043$) also significantly decreased bilaterally. Computed tomography images showed a significant increase in the cross-sectional area of the abdominal, trunk, and thigh muscles but not in that of the lower leg muscles after the supervised exercise program intervention.

Conclusions: In this study, bicycle exercise training improved the QOL and walking distance and decreased hip movement. The results showed that bicycling might be as useful as walking in patients with PAD. (J Vasc Surg 2019;■:1-9.)

Keywords: Exercise training; Intermittent claudication; Peripheral artery disease; Walking efficacy

Intermittent claudication (IC) is one of the symptoms of peripheral artery disease (PAD) that could disturb daily activities and athletic performance. Treatment of IC includes medication, surgical intervention, and exercise training. Among them, exercise training is less invasive, inexpensive, and recognized as the first-line therapy for IC.

The effects of exercise training on PAD patients have been previously studied. Meta-analyses of randomized trials reported that walking distance increases >100% after exercise training.[1,2] Moreover, exercise training leads to significant improvements in walking performance, physical activity, and perceived quality of life (QOL) in patients with PAD and IC.[3] The potential mechanisms for this improvement are explained by various factors, namely, collateral circulation,[4-6] endothelial function,[7,8] muscle metabolism,[9-11] hemorheology,[12,13] walking economy,[10,14,15] and inflammatory responses.[16-18] Several studies have reported an association between vascular function and structure in the process of exercise training, which has been well reviewed by Green et al.[19]

The quality and quantity of gait muscles are other contributing factors to the improvement of walking ability. The mechanisms of impaired muscle strength in PAD patients have not yet been clarified. As study hypothesis, gait muscles and relevant joint movement might be affected after the exercise training, which would contribute to improvements in walking ability.

An efficient computational algorithm for multibody systems was previously developed and applied to the musculoskeletal model of the human body.[20] It was assumed that the inverse dynamics method, which is a method for computing forces and moments of forces (torques) based on kinematics, and the computation of a musculoskeletal human model using motion capture data would aid in elucidating the mechanisms underlying PAD improvements after exercise training.

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This study aimed to examine the effects of a 3-month supervised exercise program (SEP) on lower limb and trunk movement variability in IC patients and to evaluate lower extremity kinematics and muscle morphology before and after the SEP intervention.

METHODS

Participants. All patients who attended an outpatient clinic of a vascular surgery unit in Tokyo, Japan, between January 2013 and December 2015 were screened for the study. Patients were diagnosed as having PAD according to their history of claudication and if they had an ankle-brachial index (ABI) $<$0.9. Patients with critical limb ischemia (rest pain or tissue loss), history of ischemic heart disease or cerebral infarction, neurologic or musculoskeletal disorders, and dementia and those aged $>$80 years with limited gait and balancing ability were excluded. Near-infrared spectroscopy (NIRS) is useful for evaluating the function of the extremities in PAD patients.[21,22] It is not an invasive modality, and it was used routinely for claudicants in this study. A key parameter of NIRS is the recovery time of oxygenated and deoxygenated hemoglobin from the end of the walk to baseline. Recovery time was reported to be correlated with the severity of IC.[21] Calf muscle hemoglobin oxygen saturation (So_2) was also shown in NIRS, and it primarily reflects the relative balance between oxygen delivery and oxygen utilization of local tissue.[23] In this study, to evaluate ischemic changes in calf muscles, differences in So_2 before and after SEP intervention were compared.

Computed tomography (CT) angiography (Aquilion; Toshiba, Tokyo, Japan) was performed in all participants for analysis of disease anatomy and mass. The transverse CT image of the lower border of the third lumbar vertebra was assessed in each patient. The rectus abdominis, abdominal oblique, psoas major, and erector spinae muscles were evaluated as previously described.[24,25] The transverse CT image of the lower end of the ischial bone and middle of the fibula was assessed in each patient to analyze the rectus femoris, gluteus maximus, and lower leg muscles. Cross-sectional areas of each muscle were measured by manually outlining the CT images using software (Aquarius iNtuition; TeraRecon, Tokyo, Japan; Fig 1). The field range of the cross section was determined through discussion between M.K. and K.H.; thereafter, M.K. measured the field. ABI, NIRS, and CT angiography were performed before and after the SEP intervention.

All patients provided written informed consent. The protocol was approved by the institutional Research Ethics Committee of The University of Tokyo Hospital (No. 10208-(2)).

Exercise program protocol. All enrolled participants underwent a 3-month SEP conducted in the vascular unit of our hospital and performed using a bicycle ergometer (Aerobike 900U; Konami, Tokyo, Japan). A bicycle ergometer in the cardiac rehabilitation program was used, in which a treadmill was not included. The program consisted of a bicycling exercise 3 days per week. Exercise intensity was set at 70% of maximal load with 30 minutes per session. The exercise protocol also incorporated warm-up and cool-down sessions that involved stretches of the major lower limb muscle groups (total exercise time, 40-60 minutes).

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center prospective cohort study
- **Key Findings:** No significant differences were noted in step length, ankle-brachial index, and oxygen saturation before and after a 3-month supervised exercise program in 16 patients with claudication. On the contrary, intermittent claudication distance, maximum walking distance, and quality of life questionnaire scores showed significant improvement after the exercise intervention.
- **Take Home Message:** Bicycle exercise training improved the quality of life and walking distance; less hip movement was found in patients with peripheral artery disease.

Data acquisition and procedures. Twelve cameras (Raptor-4, Eagle; Motion Analysis, Santa Rosa, Calif) were used to collect the kinematic and kinetic data of patients during continuous walking on a treadmill (Daikou DK-8421B; Kobe Medicare, Kobe, Japan). Participants wore comfortable clothes and shoes for testing. Thirty-five markers were set on the body surface to capture the kinematic data (Fig 2). The participants were instructed to walk continuously on the treadmill at a speed of 2.4 or 3.6 km/h until they could not continue because of exhaustion or pain, and they were instructed to inform the investigator when claudication symptoms developed. At this point, three outcomes (step length, distance until IC, and maximum walking distance) were recorded. These data were collected before and after the SEP intervention at the laboratory of our institution where the treadmill was available for use. These features were not analyzed with structured walking because kinematic data could be accurately collected by walking on the treadmill at the same speed.

QOL scores. QOL before and after the exercise program was evaluated with two QOL measures. Walking distance, walking speed, and stair climbing were reported as three domains of the Walking Impairment Questionnaire, a PAD-specific measure of self-reported limitations.[26] Each domain is scored on a scale of 0 to 100 points, wherein 0 represents extreme limitation and 100 represents no difficulty in walking long distances, walking rapidly, or

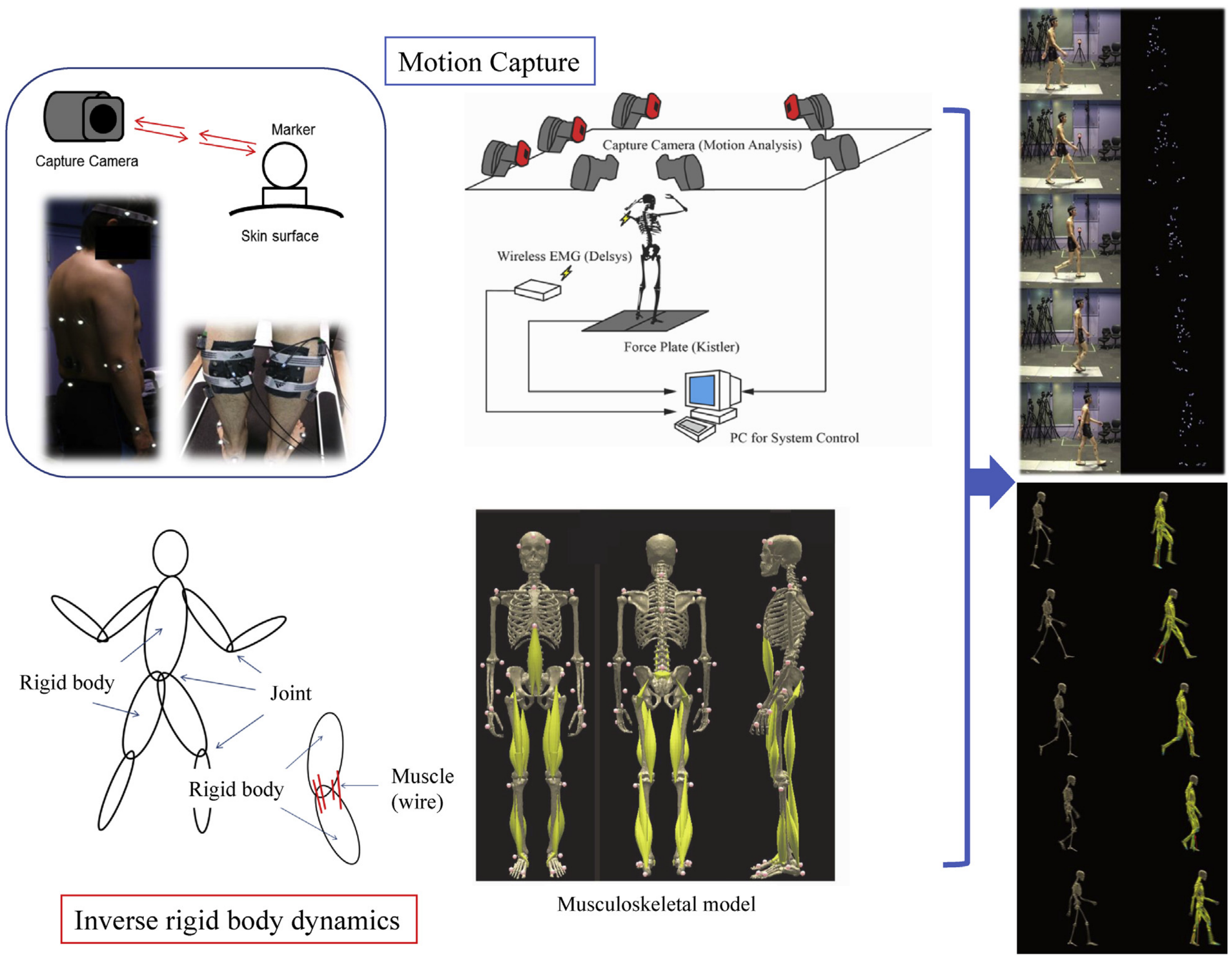

Fig 1. Gait data were processed using a software program to determine the position of markers. The musculoskeletal model was applied to analyze the kinematics and dynamics of each motion. *EMG,* Electromyography; *PC,* personal computer.

climbing three flights of stairs.[26] The Vascular Quality of Life questionnaire is a disease-specific measure of QOL specifically developed for assessing PAD patients and is also sensitive to within-patient changes.[27,28]

Motion capture data analysis. Gait characteristics were identified using kinematic and kinetic data as previously described. A visual three-dimensional motion analysis software was used (Cortex; Motion Analysis) to determine the sequence of the three-dimensional positions for the markers. A musculoskeletal model was applied to analyze the kinematics and dynamics of each patient's motion[20] (Fig 2). Inverse kinematics computation with the kinematic properties determined the joint angle sequence. The measured joints were the hip, knee, and ankle. The maximum range of motion (ROM) of each joint angle was analyzed. Inverse dynamic computation and the inertial properties of each patient were used to compute the generated forces, which correspond to the joint torques. Mathematical optimization was carried out to distribute the joint angles to the joint torques and then to the muscle maximum tensions. The evaluation function of inverse kinematics analysis and inverse dynamics analysis were used to calculate the optimum joint angle and force. Joint torques were analyzed by integrating the average of one cycle. All data were normalized to a 1.0 gait cycle. Motion capture data were collected before and after the SEP.

Statistics. Statistical analysis was performed using JMP Pro software (version 11.2.1; SAS Institute, Cary, NC). Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean ± standard deviation or standard error. Group differences were evaluated using the paired *t*-test for continuous variables with JMP Pro software. Statistical significance was defined as $P < .05$.

RESULTS

Nineteen IC patients were recruited for this study. Three patients were excluded from the analysis because of worsened IC, brain infarction, and intolerance of the

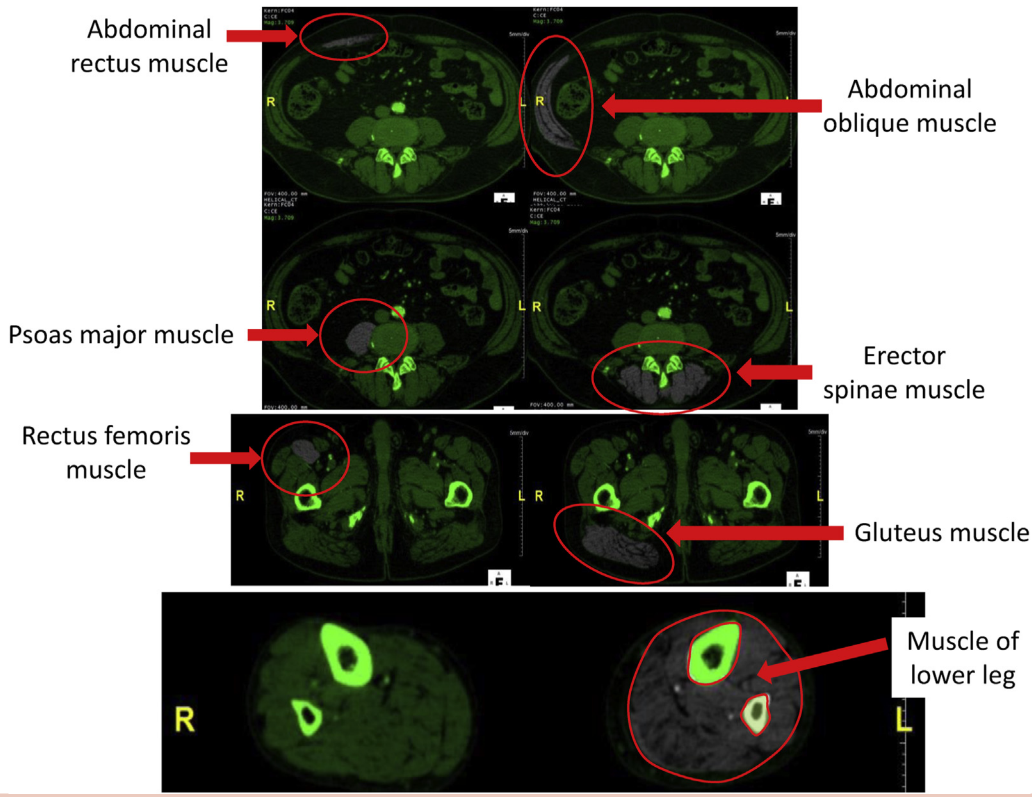

Fig 2. Computed tomography (CT) showing the area of skeletal muscle in each region (*gray*). The abdominal rectus muscle, abdominal oblique muscle, psoas major muscle, erector spinae muscle, rectus femoris muscle, gluteus muscle, and calf muscles were analyzed.

SEP. A summary of the patients' (n = 16) characteristics is shown in Table I. IC symptoms appeared on the lower leg of 11 patients and on the whole lower extremity of five patients. The occlusion or stenosis was located on the aortoiliac region in six patients and on the superficial femoral artery-popliteal region in 10 patients. Six patients had bilateral lesions.

PAD features are shown in Table II. No significant differences were found in step length, ABI, and So_2; however, IC distance (P = .034), maximum walking distance (P = .006), and all QOL questionnaire scores (P < .001) showed significant improvement after the SEP. Hip ROM (P = .035) and maximum hip torque (right, P = .031; left, P = .044) significantly decreased bilaterally. The maximum tension of the gluteus maximus muscle (right, P = .044; left, P = .042) and the maximum hip joint work (right, P = .048; left, P = .043) significantly decreased bilaterally (Table II).

Cross-sectional CT images showed a significant increase in abdominal (abdominal rectus, P < .001; abdominal oblique, P = .023), trunk (psoas major, P = .005; erector spinae, P = .004), gluteus (right, P = .006; left, P = .016), and thigh (rectus femoris: right, P = .026; left, P = .012) muscles. However, this was not observed in the lower leg muscles (Table III).

Changes in kinematics after the SEP can be seen in further detail in Videos 1 and 2 (online only).

DISCUSSION

After a 3-month structured exercise program using a bicycle ergometer, this study reported improvement in walking distance and questionnaire scores for patients with PAD and IC; however, no improvement was found in the other parameters (step length, ABI, and hemoglobin oxygen saturation). In addition, the effect of SEP was proven by analysis of the motion capture system (decrease in the hip ROM, hip joint torque, hip joint work, and maximum muscle tension of the gluteus maximus) and CT imaging (increase in the cross-sectional area of the abdomen, trunk, and thigh muscles, although not in the lower leg muscles).

Impaired walking ability in IC patients may be a consequence of reduced leg muscle strength and endurance. The mechanisms that explain impaired muscle strength in PAD patients have not been fully elucidated. Therefore, it was initially assumed that exercise training would affect the muscle tension and relevant joint movements, resulting in improved walking ability. Although the muscle mass of the lumbar major muscle and thigh muscles increased with exercise training, there was less movement at the hip area after the SEP, indicating that the walking technique (including postural stability and walking economy) could be contributing more to the gait improvement than physiologic changes.

Table I. Characteristics of the study participants

	PAD patients (n = 16)
Age, years	71.4 ± 6.0
Sex, male:female	13:3
BMI, kg/m^2	23.2 ± 3.1
Ex-smoker	8 (50)
Anatomic division	
Aortoiliac	6 (37.5)
SFA-popliteal	10 (62.5)
Location of IC, right:left	9:7
Rutherford I	16 (100)
Diseases	
Hypertension	12 (75)
Hyperlipidemia	9 (56)
Diabetes mellitus	12 (75)
Ischemic cardiac disease	4 (25)
Cerebrovascular disease	1 (6.2)
Spinal stenosis	3 (18)
Medication	
Antiplatelet agent	16 (100)
Statin	8 (50)
Beta inhibitor	4 (25)
ACE inhibitor	2 (12)
ARBs	9 (56)
Calcium antagonist	7 (46)

ACE, Angiotensin-converting enzyme; *ARBs,* angiotensin II receptor blockers; *BMI,* body mass index; *IC,* intermittent claudication; *PAD,* peripheral artery disease; *SFA,* superficial femoral artery.
Categorical variables are presented as number (%). Continuous variables are presented as mean ± standard deviation.

There is one possible mechanism that may be considered to explain the effects of the SEP intervention in gait parameters. The muscles evaluated in this study (rectus abdominis, iliopsoas, erector spinae, rectus femoris, gluteus maximus) perform antigravity activity,[29] and the increase in their cross-sectional area should increase the stability of the standing posture. In exercise physiology, "efficient walking" is defined as walking with less movement of the center of gravity.[30] The center of gravity in humans is located in front of the sacrum and moves periodically in the left, right, and vertical direction during walking.[30,31] Walking with less periodic change involves less change in the center of gravity.[30,31] A postural stabilization effect of the SEP would lead to lower energy expenditure compared with the pre-SEP state. Walking with less energy decreases the hip joint movement range, hip joint torque, and maximum muscle tension of the gluteus maximus muscle, which leads to an improvement in walking ability. In this study, changes in the center of gravity before and after exercise training could not be verified; therefore, gait efficiency was not completely proven. Cavagna et al[30] advocated analyzing the change in kinetic energy as a function of the position energy and kinetic energy of the center of gravity. Proving energy efficiency by focusing on the change in kinetic energy with normal controls is warranted in the future.

This study did report the kinematic and muscle changes; however, this could be due to some physiologic changes (ie, improvement in the flow-mediated dilation of the patients' arterial vasculature and consequent improved walking tolerance) caused by the SEP, leading to better kinematics and thus improved muscle volume. These findings might constitute independent changes or combined biologic responses to SEP. However, there is no way to explain the exact mechanism for this improvement.

Previous studies on motion analysis for PAD patients reported symptomatic improvement; however, they did not reveal a clear mechanism. Crowther et al[32] reported no significant effect on lower limb movement variability after an SEP. This might be because a two-dimensional capture technique was used in that study, which has been reported to increase measurement error.[33] King et al[34] also failed to show significant changes in any of the gait parameters after an SEP, including peak hip extension, peak ankle plantar flexion, and peak vertical ground reaction force, which might be due to the lack of detailed muscle and biomechanical adaptations. The results of this study were obtained by both the three-dimensional motion capture system and detailed musculoskeletal analysis.

In the evaluation and measurement of the muscle cross-sectional area on CT images, the modified method of previous reports was adopted for this study. The third lumbar vertebra is often used as a positional reference for tracing the muscle contour on the CT transverse image, with high reliability.[24,25] In addition to this standard index, the lower end of the ischial bone and the middle part of the fibula were evaluated as measurement standards in this study because the gluteus maximus, rectus femoris, and lower leg muscles were to be evaluated, which cannot be assessed by image evaluation at the position of the third lumbar vertebra.

The point of this study is that SEP was performed by using a bicycle ergometer. The efficacy of bicycle exercise training is not well understood. On the contrary, the effects of walking have been widely reported.[35-38] In one of these studies, Parmenter et al[37] reported that the strength of the lumbar and femoral muscles increased 1.42 times after training. In contrast, exercise training using a bicycle ergometer mainly affects the rectus femoris and biceps femoris.[39] This study showed an increase in the cross-sectional area of the lumbar and femoral muscles, but no changes were found in the cross-sectional area of the lower leg muscles. The lower leg muscles are more exposed to ischemia; therefore, they have a reduced oxygen supply, decreasing protein synthesis ability. Accordingly, the strengthening

Table II. Parameters of peripheral artery disease (*PAD*) and muscle maximum tension and joint work

	Before SEP	After SEP	*P* value
Parameters of PAD			
ABI			
Right	0.79 ± 0.19	0.77 ± 0.20	.189
Left	0.77 ± 0.21	0.76 ± 0.19	.621
Parameter of NIRS			
Recovery time, seconds	200.1 ± 151.6	143.1 ± 104.8	.144
Right ΔSo_2, %	16.1 ± 12.6	14.0 ± 12.7	.847
Left ΔSo_2, %	17.7 ± 12.8	17.8 ± 13.3	.947
QOL score			
VascuQOL	4.2 ± 0.9	5.7 ± 0.6	<.001
WIQ distance score	68.7 ± 19.6	89.7 ± 14.6	<.001
WIQ speed score	29.2 ± 13.3	61.2 ± 20.0	<.001
WIQ climbing score	35.9 ± 18.4	76.0 ± 23.9	<.001
Right leg step length, m	0.50 ± 0.08	0.50 ± 0.08	.664
Left leg step lengths, m	0.51 ± 0.09	0.50 ± 0.08	.872
Length of IC with the treadmill, m	160 ± 128	228 ± 187	.034
Maximum walking distance, m	453 ± 345	702 ± 416	.006
Joint angles, degrees			
Right			
Hip max	−13.6 ± 8.2	−13.2 ± 9.4	.826
Hip ROM	39.4 ± 5.6	37.6 ± 5.3	.035
Knee max	60.7 ± 6.4	60.8 ± 6.7	.951
Knee ROM	57.8 ± 6.7	56.6 ± 5.3	.327
Ankle max	13.7 ± 5.3	13.2 ± 5.5	.757
Ankle ROM	21.8 ± 5.1	22.4 ± 6.4	.671
Left			
Hip max	−13.7 ± 8.2	−13.3 ± 9.3	.757
Hip ROM	39.2 ± 5.5	37.7 ± 5.1	.037
Knee max	60.7 ± 6.4	61.2 ± 6.2	.792
Knee ROM	57.9 ± 7.0	57.1 ± 4.9	.505
Ankle max	13.7 ± 5.3	12.7 ± 6.4	.608
Ankle ROM	21.7 ± 5.0	21.5± 8.2	.866
Maximum joint torque, N			
Right			
Hip	88.0 ± 18.8	83.5 ± 19.7	.031
Knee	62.5 ± 17.7	56.8 ± 17.7	.251
Ankle	133.4 ± 20.1	131.5 ± 26.1	.759
Left			
Hip	88.1 ± 18.5	83.5 ± 20.2	.044
Knee	62.3 ± 17.2	56.3 ± 17.6	.213
Ankle	132.6 ± 18.7	131.1 ± 25.6	.813
Muscle maximum tension and joint work			
Muscles maximum tension, N			
Right			
Multifidus muscle	312.2 ± 116.9	329.0 ± 137.6	.611
Gluteus maximus	167.6 ± 31.6	149.8 ± 44.2	.044
Rectus femoris	980.1 ± 151.7	961.8 ± 221.5	.541
Vastus intermedius	544.0 ± 296.2	743.3 ± 447.0	.091

Table II. Continued.

	Before SEP	After SEP	*P* value
Semimembranosus	969.5 ± 114.4	931.9 ± 128.2	.225
Gastrocnemius	639.0 ± 9.3	638.4 ± 13.0	.798
Soleus	2000.3 ± 131.1	2027.4 ± 119.2	.547
Anterior tibial	800.9 ± 23.6	800.2 ± 50.0	.957
Left			
Multifidus muscle	313.6 ± 116.0	327.4 ± 139.4	.683
Gluteus maximus	167.5 ± 31.5	149.3 ± 44.6	.042
Rectus femoris	980.0 ± 149.4	962.8 ± 219.6	.561
Vastus intermedius	551.9 ± 301.5	734.8 ± 453.7	.122
Semimembranosus	966.6 ± 118.3	935.2 ± 128.5	.314
Gastrocnemius	638.9 ± 9.2	638.8 ± 12.8	.974
Soleus	2028.1 ± 107.2	2027.6 ± 120.2	.989
Anterior tibial	801.0 ± 23.6	799.7 ± 50.0	.917
Joint work, Nm			
Right			
Hip	87.2 ± 20.0	81.6 ± 20.4	.048
Knee	62.5 ± 17.7	56.8 ± 17.7	.193
Ankle	133.4 ± 20.1	131.5 ± 26.1	.410
Left			
Hip	87.3 ± 19.7	81.6 ± 20.9	.043
Knee	62.3 ± 17.2	56.3 ± 17.6	.111
Ankle	132.6 ± 18.7	131.1 ± 25.6	.319

ABI, Ankle-brachial index; *IC*, intermittent claudication; *NIRS*, near-infrared spectroscopy; *ROM*, range of motion; So_2, oxygen saturation; *SEP*, supervised exercise program; *VascuQoL*, Vascular Quality of Life questionnaire; *WIQ*, Walking Impairment Questionnaire.
Values are reported as mean ± standard deviation.

Table III. Outlining computed tomography (CT) images of skeletal muscle area before and after intervention

Muscle	Before SEP, cm^2	After SEP, cm^2	Change, %	*P* value
Abdominal rectus	8.4 ± 2.8	9.3 ± 3.2	19.2	<.001
Abdominal oblique	35.2 ± 12.8	37.4 ± 12.4	7.1	.023
Psoas major	20.1 ± 4.7	21.4 ± 4.9	7.1	.005
Erector spinae	33.7 ± 9.0	35.3 ± 9.6	4.5	.004
Right gluteus	34.1 ± 7.0	36.7 ± 8.3	7.1	.006
Left gluteus	32.7 ± 8.1	36.1 ± 9.1	10.4	.016
Right rectus femoris	7.7 ± 2.3	8.3 ± 2.1	10.7	.026
Left rectus femoris	7.2 ± 1.7	8.0 ± 1.9	11.9	.012
Right lower leg	45.7 ± 10.4	45.6 ± 10.9	0.3	.961
Left lower leg	43.9 ± 8.8	44.8 ± 8.8	2.1	.389

SEP, Supervised exercise program.
Values are reported as mean ± standard deviation.

effect might be smaller in the lower leg than in the thigh. These findings show that bicycle training might be as useful as walking. In addition, a new method of exercise training, concentrating only on hip pumping to help hip joint movement, might contribute to improving walking ability without performing walking exercise training. Further studies need to assess this speculation in the future.

Changes in ABI, NIRS, and other important parameters were not observed in this study. However, exercise training has not been found to improve ABI in claudication patients.[40] To reveal the mechanism, analysis with other modalities, such as angiography and plethysmography, is warranted in the future.

This study has some limitations. First, a certain degree of error should be inevitable in this three-dimensional motion analysis. In the current system, patients' height and weight were used to optimize the model correspondence to patients' physique. However, the number of joints reproduced in the musculoskeletal model was 155.[41] To increase model precision, more parameters should be included, and improved calculations are necessary.

A second limitation is the adequacy of the inverse kinematics analysis and inverse dynamics analysis. According to the calculation of inverse dynamics in previous reports, the evaluation function of inverse kinematics analysis is the mainstream nonlinear optimization method to obtain the coordinates that minimize the error from the target position.[41,42] However, few previous studies have determined muscle tension from torque by inverse dynamics analysis. The evaluation function of inverse dynamics analysis is a theoretically derived solution method; however, further verification is warranted because it is not yet an established method.

Third, the maximum voluntary strength could not be measured, which is considered to accurately reflect the strength of each muscle. For the measurement of the maximum voluntary strength, an isokinetic or isometric dynamometer would be required.

CONCLUSIONS

Bicycle exercise training improved the QOL and walking distance and decreased hip movement. The results of this study suggest that bicycle training might be as useful as walking exercise training in PAD patients.

AUTHOR CONTRIBUTIONS

Conception and design: MH, KH, HK, TM, YI, AM, YN
Analysis and interpretation: MH, KH
Data collection: YI, AM
Writing the article: MH, KH, YI
Critical revision of the article: KH, HK, TM, YI, AM, YN
Final approval of the article: MH, KH, HK, TM, YI, AM, YN
Statistical analysis: MH
Obtained funding: Not applicable
Overall responsibility: KH

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