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Muscle forces and power are significantly reduced during walking in patients with peripheral artery disease

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Muscle forces and power are significantly reduced during walking in patients with peripheral artery disease

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A B S T R A C T

Patients with peripheral artery disease (PAD) have significantly reduced lower extremity muscle strength compared with healthy individuals as measured during isolated, single plane joint motion by isometric and isokinetic strength dynamometers. Alterations to the force contribution of muscles during walking caused by PAD are not well understood. Therefore, this study used simulations with PAD biomechanics data to understand lower extremity muscle functions in patients with PAD during walking and to compare that with healthy older individuals. A total of 12 patients with PAD and 10 age-matched healthy older controls walked across a 10-meter pathway with reflective markers on their lower limbs. Marker coordinates and ground reaction forces were recorded and exported to OpenSim software to perform gait simulations. Walking velocity, joint angles, muscle force, muscle power, and metabolic rate were calculated and compared between patients with PAD and healthy older controls. Our results suggest that patients with PAD walked slower with less hip extension during pro- pulsion. Significant force and power reductions were observed in knee extensors during weight acceptance and in plantar flexors and hip flexors during propulsion in patients with PAD. The estimated metabolic rate of walking during stance was not different between patients with PAD and controls. This study is the first to analyze lower limb muscular responses during walking in patients with PAD using the OpenSim simulation software. The simulation results of this study identified important information about alterations to muscle force and power during walking in those with PAD.

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1.Introduction

Peripheral artery disease (PAD) is a common cardiovascular disorder resulting from atherosclerosis of the lower extremities that leads to reduced leg blood flow. The most common symptom of PAD is intermittent claudication, defined as cramping pain that occurs in the calves, thighs, and/or buttocks, brought on by physical activity and relieved with rest. Patients with PAD have altered walking performance, reduced quality of life, a progressively sedentary lifestyle, and higher risk of mortality compared to individuals of similar age without PAD (Celis et al., 2009; Gardner and Montgomery, 2001; Hernandez et al., 2019; Koutakis et al., 2010b; McDermott, 2013; Rahman et al., 2021b; Sieminski and Gardner, 1997). Previous work suggests abnormal lower extremity blood flow and underlying cellular abnormalities in the lower extremity muscles and nerves contribute to differences prior to pain onset (Celis et al., 2009; Koutakis et al., 2015a, 2015b; Myers et al., 2011; Rahman et al., 2021b).

Biopsy studies from gastrocnemius calf muscles taken from patients with PAD have identified altered myofiber morphology and a related muscle myopathy (Koutakis et al., 2015a, 2015b). These findings align with the significantly reduced muscle strength in the lower extremities of patients with PAD compared to healthy controls (McDermott et al., 2004; Schieber et al., 2017; Scott-Okafor et al., 2001). While peak strength may provide useful insights, these results only represent the changes in muscle strength during isolated, single plane joint motion as assessed with isometric strength testing (ankle plantarflexion/dorsi- flexion, knee flexion/extension, hip flexion/extension). A more representative measurement would be from functional muscular responses that people would typically experience while performing daily activities (McDermott et al., 2004; Schieber et al., 2017; Scott-Okafor et al., 2001). The forces generated by lower extremity muscles during activities of daily living, such as walking, are more representative than single plane joint motion. Identifying alterations in lower leg muscle force activation patterns in the presence of PAD may provide useful information regarding muscle loading distributions during walking. This information may further assist in developing treatment and rehabilitation strategies for patients with PAD.

Musculoskeletal modeling and simulation may be able to bridge this gap because simulations can estimate how muscles generate forces during any activity. Modeling and simulation have emerged as important tools in clinical gait biomechanics. Researchers have successfully applied modeling to improve surgical methods and rehabilitation programs targeted towards neurological and musculoskeletal impairments (Rosenberg and Steele, 2017). Thus, a musculoskeletal modeling approach provides important insight into changes to muscle force generation during walking caused by the presence of PAD. Understanding changes in muscle force activation during walking is important for designing interventions and assistive devices to restore function in patients with PAD.

Therefore, the aim of this study was to investigate lower extremity muscle function in patients with PAD during walking using musculoskeletal modeling and simulations and to compare muscle function in patients with PAD to healthy older individuals.

2.Methods

2.1. Patient characteristics

The study was approved by the Institutional Review Boards at the Nebraska-Western Iowa Veteran Affairs Medical Center and the University of Nebraska Medical Center. Two groups of subjects were enrolled for this study: 1) patients with PAD, and 2) healthy older controls. A total of 12 patients (age: 67.08 ± 5.85 years, body mass: 93.55 ± 18.19 kg, body mass index: 30.60 ± 6 kg/m^2) diagnosed with Fontaine stage II PAD were screened by one of two board-certified vascular surgeons and recruited through the vascular surgery clinics of these institutions. All patients were free from any gait altering musculoskeletal or neurological conditions other than PAD that limited or altered walking. A total of 10 age-matched healthy older control subjects (age: 65.80 ± 8.61 years, body mass: 87.55 ± 10.55 kg, body mass index: 27.60 ± 3.06 kg/m^2) were recruited from the surrounding com- munity. All healthy older control subjects had an ankle-brachial index ≥ 1.0 and had no diseases that could cause ambulatory dysfunction. All subjects provided informed consent before study participation.

2.2. Experimental data collection

Experimental tests were conducted at the Biomechanics Research Building at the University of Nebraska at Omaha. Reflective markers were placed on specific anatomical locations of each subject's lower limbs, utilizing the systems used by Vaughan (Vaughan et al., 1999) and Nigg (Nigg et al., 1993). Details can be found in previously published articles from our group (Celis et al., 2009; Koutakis et al., 2010b). Each subject walked across a 10-meter pathway with force plates mounted level with the ground without any claudication pain (pain free walking). The coordinates of the markers and ground reaction forces were recorded using a 12-high speed infrared camera system (60 Hz, Motion Analysis Corporation, Rohnert Park, CA) and force plates (600 Hz, AMTI, Watertown, MA), respectively.

2.3. Musculoskeletal modeling and simulation

Gait simulations were performed in OpenSim version 4.0, an open- source musculoskeletal modeling and simulation platform (Delp et al., 2007). A generic 'Full Body Musculoskeletal Model' was used to perform the walking simulations (Rajagopal et al., 2016). First, the anthropometry of the model was individually matched to that of each subject using the 'Scale' tool in OpenSim. Experimental marker data were fed into the 'Inverse Kinematics' tool to calculate joint angles by minimizing errors between the experimental marker trajectories and virtual markers on the scaled model. Joint angles obtained from the 'Inverse Kinematics' tool for walking trials were imported into the 'Residual Reduction Algorithm (RRA)' tool. The RRA alters the torso mass center and changes the kinematics

to minimize the dynamic inconsistencies between recorded ground reaction forces and calculated residual forces. Then, the kinematics from the RRA were exported into the 'Computed Muscle Control (CMC)' tool to calculate the individual muscle forces. A metabolic probe was added to the muscles in the model to calculate the energy consumption of each muscle (Uchida et al., 2016; Umberger, 2010; Umberger et al., 2003). This metabolic probe estimates the rate of muscle energy expenditure for each muscle by considering activation heat rate, maintenance heat rate, shortening/lengthening heat rate, and mechanical work rate of the contractile elements in the muscle model (Umberger et al., 2003).

2.4. Data processing

The walking velocity for each subject was calculated as the average distance traveled per second from at least 3-consecutive steps based on the coordinates of reflective markers, as explained in previously published articles from our group (McCamley et al., 2019; Rahman et al., 2021a; Wurdeman et al., 2012). In five patients who had unilateral PAD, we included the PAD leg for analysis. For those who had bilateral PAD (seven patients), we analyzed only the most affected leg based on their ankle-brachial index. We performed randomization for the legs of the control subjects to determine whether to analyze the right or left leg. The time series data obtained from the OpenSim were resampled to 1000 data points and expressed as a percentage of stance, which is defined as the portion of gait between heel-strike and toe-off of the analyzed leg (Koutakis et al., 2010a). The resampling was done to ensure that each relative time point could be compared between subjects and groups. The muscle force and power were normalized by subjects' bodyweight in newtons and kilograms and were reported as bodyweights (BW) and Watts/kg (W/kg), respectively. The metabolic rate (energy consumption rate) data were exported as the sum of all muscles that exist in the OpenSim model and were normalized by the subjects' mass in kilograms and reported in Watts/kg (W/Kg). Total energy expenditure during stance was calculated as the area under the curve of the aggregated metabolic rate time series made from all the muscles in the model and was reported in Joules/Kg (J/Kg). Data processing and analyses were performed using custom codes in MATLAB (The MathWorks Inc., Natick, MA) and Python (Python Software Foundation, DE).

2.5. Statistical analysis

Descriptive statistics were conducted for all variables. Discrete local maximums and minimums were selected along regions in the time series for comparison between the PAD and control groups. The criterion for designating regions for locating extrema was that all subjects had to express the extrema of interest in the respective regions. Local extrema were then manually extracted from the designated regions by selecting the local minimums and maximums graphically in MATLAB. The local extrema along the various time series for each subject were compiled and included in the statistical analysis. The normality of the data was assessed using the Shapiro-Wilk test and normality plots. All the variables were normally distributed. Therefore, we used unpaired t-tests to detect

differences between groups (patients with PAD vs healthy older controls) (Celis et al., 2009; Kulmala et al., 2020; Wurdeman et al., 2012). A *p*-value < 0.05 was considered statistically significant. Allstatistics were performed in GraphPad Prism software (version9.0.2, GraphPad Software, San Diego, California).

3.Results

3.1. Joint kinematics

The maximum ankle angle, A_{max}, during stance did not significantly differ between patients with PAD and healthy older controls (Δ = 0.53 ± 6.14°, *p* = 0.779; Fig. 1A, Table 1). For knee kinematics, the first local maximum during weight acceptance, K_{max}, and the local minimum near toe-off, K_{min}, were not different between patients with PAD and controls (Δ = − 1.88 ± 5.49°, *p* = 0.272, Δ = 3.45 ± 6.33°, *p* = 0.091, respectively; Fig. 1B, Table 1). However, maximum hip extension, H_{min}, during late stance was lower in patients PAD compared to controls (Δ = 6.71 ± 8.42°, *p* = 0.016; Fig. 1C, Table 1).

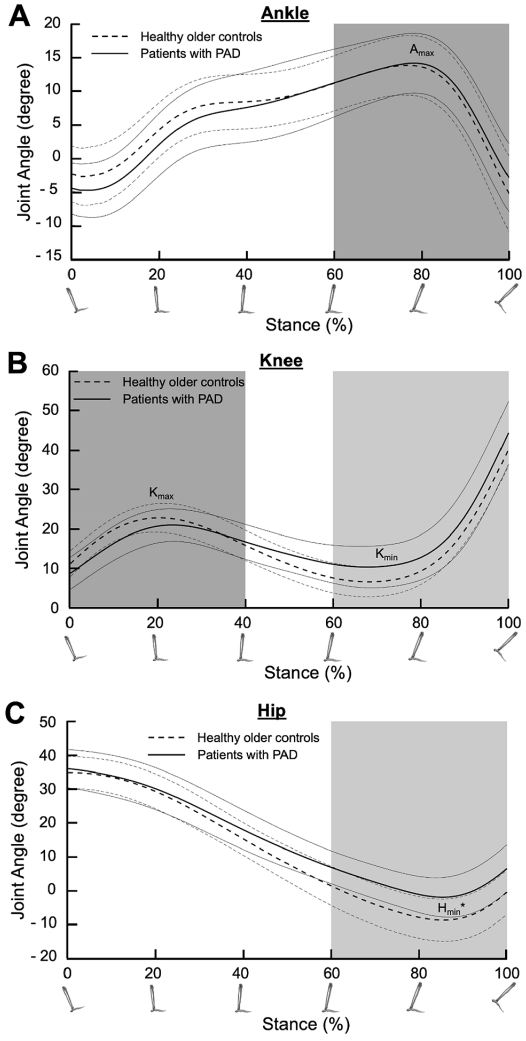

Fig. 1. A) Ankle, B) knee, and C) hip joint angles for healthy older controls and patients with peripheral artery disease (PAD) during stance phase. The dark solid line and the dark dotted line represent the joint angles for patients with PAD and healthy older controls, respectively. The grey solid lines and the grey dotted lines represent one standard deviation from the average values. The dark grey shaded regions are time ranges where a local maximum (peak) was selected, and the light grey regions are time ranges where a local minimum was selected. Local extrema were selected manually for each subject and compiled for statistical analysis. * indicates a significant difference between patients with PAD and healthy older controls ($p < 0.05$). A_{max}, maximum ankle angle; K_{max}, maximum knee angle, K_{min}, minimum knee angle; H_{min}, maximum hip extension.

Table 1. Group means for maximum and minimum joint angles for patients with peripheral artery disease (PAD) and healthy older controls (CON) groups.

Kinematics (°)	PAD	CON	Δ = (PAD – CON)	*p*-value
A_{max}	14.45 ± 4.27	13.92 ± 4.41	0.53 ± 6.14	0.779
K_{max}	21.17 ± 4.00	23.05 ± 3.76	− 1.88 ± 5.49	0.272
K_{min}	9.81 ± 5.05	6.36 ± 3.82	3.45 ± 6.33	0.091
H_{min}	− 1.97 ± 5.76	− 8.68 ± 6.15	6.71 ± 8.42	0.016*

Values are shown as Mean ± Standard deviation.

*Significant differences between PAD and CON.

Δ, differences between PAD and CON; A_{max}, maximum ankle angle; K_{max}, maximum knee angle, K_{min}, minimum knee angle; H_{min}, maximum hip extension.

3.2. Walking velocity

Patients with PAD had a slower walking velocity compared to con- trols (PAD: 1.04 ± 0.16 m/s, Controls: 1.27 ± 0.09 m/s, $p < 0.001$).

3.3. Ankle plantar flexors

Although peak plantar flexor force, PFF_{peak}, was not different be- tween patients with PAD and controls (Δ = - 0.47 ± 1.17 BW, $p = 0.199$; Fig. 2A, Table 2), there was significant attenuation in the peak lateral gastrocnemius muscle force, LGF_{peak}, and peak medial gastrocnemius muscle force, MGF_{peak}, during propulsion (LGF_{peak}: Δ = - 0.25 ± 0.39 BW, $p = 0.039$; MGF_{peak}: Δ = - 0.63 ± 0.84 BW, $p = 0.022$; Fig. 2B & 2C, Table 2). However, there was not a difference in peak soleus force, $SolP_{peak}$, between groups (Δ = 0.18 ± 0.85 BW, $p = 0.499$; Fig. 2D, Table 2).

Although minimum plantar flexor power, PFP_{min}, was not different between patients with PAD and controls, peak plantar flexor power, PFP_{peak}, was lower in patients with PAD (PFP_{min}: Δ = 0.11 ± 0.28 W/kg, $p = 0.209$; PFP_{peak}: Δ = - 1.15 ± 1.73 W/kg, $p = 0.036$; Fig. 2E, Table 3). Minimum lateral gastrocnemius power, LGP_{min}, was higher in patients with PAD, whereas peak lateral gastrocnemius power, LGP_{peak}, was not different between groups (LGP_{min}: Δ = 0.05 ± 0.06 W/kg, $p = 0.012$; LGP_{peak}: Δ = - 0.27 ± 0.59 W/kg, $p = 0.132$; Fig. 2F, Table 3). In contrast, for the medial gastrocnemius muscle, minimum power, MGP_{min}, was not different between groups, but peak power, MGP_{peak}, was lower in patients with PAD (MGP_{min}: Δ = 0.12 ± 0.20 W/kg, $p = 0.057$; MGP_{peak}: Δ = - 0.92 ± 1.29 W/kg, $p = 0.022$; Fig. 2G, Table 3). However, both minimum soleus power, $SolP_{min}$, and peak soleus power, $SolP_{peak}$, were not different between patients with PAD and controls ($SolP_{min}$: Δ = - 0.10 ± 0.23 W/kg, $p = 0.167$, $SolP_{peak}$: Δ = - 0.33 ± 1.09 W/kg, $p = 0.333$; Fig. 2H, Table 3).

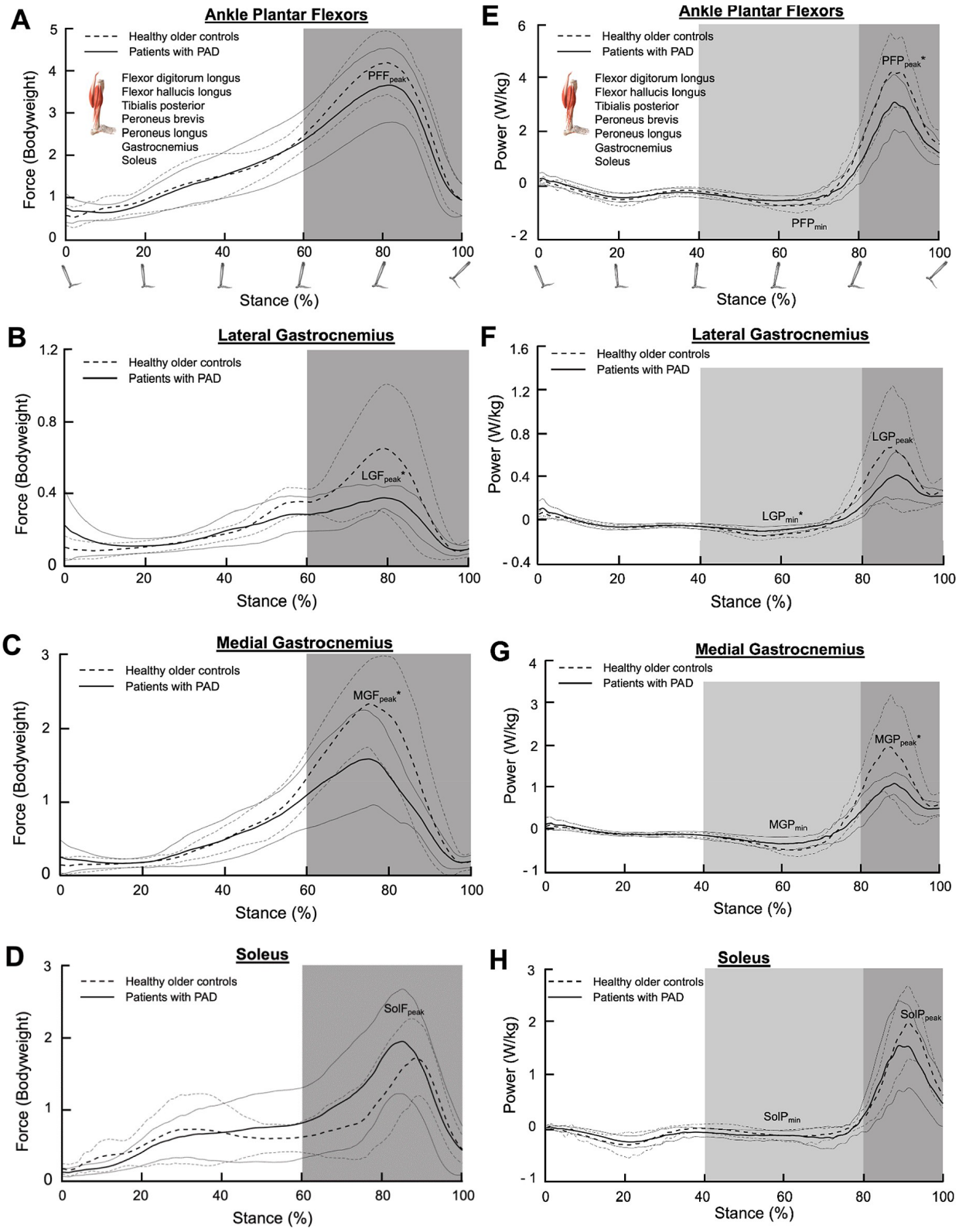

Fig. 2. Muscle forces for A) combined ankle plantar flexors, B) lateral gastrocnemius, C) medial gastrocnemius, and D) soleus during stance phase. Figures E), F), G), and H) represent the muscle power for combined ankle plantar flexors, lateral gastrocnemius, medial gastrocnemius, and soleus, respectively during stance phase. The dark solid line and the dark dotted line represent the average muscle force/power for patients with peripheral artery disease (PAD) and healthy older controls, respectively. The grey solid lines and the grey dotted lines represent one standard deviation from the average values. The dark grey shaded regions are time ranges where a local maximum (peak) was selected, and the light grey regions are time ranges where a local minimum was selected. Local extrema were selected manually for each subject and compiled for statistical analysis. * indicates a significant difference between patients with PAD and healthy older controls ($p < 0.05$). PFF_{peak}, peak plantar flexor force; LGF_{peak}, peak lateral gastrocnemius force; MGF_{peak}, peak medial gastrocnemius force; $SolF_{peak}$, peak soleus force; PFP_{min}, minimum plantar flexor power; PFP_{peak}, peak plantar flexor power; LGP_{min}, minimum lateral gastrocnemius power; LGP_{peak}, peak lateral gastrocnemius power; MGP_{min}, minimum medial gastrocnemius power; MGP_{peak}, peak medial gastrocnemius power; $SolP_{min}$, minimum soleus power; $SolP_{peak}$, peak soleus power.

Table 2. Group means for peak muscle forces for patients with peripheral artery disease (PAD) and healthy older controls (CON) groups.

Force (BW)	PAD	CON	Δ = (PAD – CON)	*p*-value
PFF_{peak}	3.76 ± 0.87	4.23 ± 0.79	− 0.47 ± 1.17	0.199
LGF_{peak}	0.43 ± 0.08	0.68 ± 0.38	− 0.25 ± 0.39	0.039*
MGF_{peak}	1.78 ± 0.54	2.41 ± 0.65	− 0.63 ± 0.84	0.022*
$SolF_{peak}$	2.07 ± 0.72	1.88 ± 0.46	0.18 ± 0.85	0.499
KEF_{peak1}	1.58 ± 0.24	1.94 ± 0.33	− 0.35 ± 0.41	0.009*
KEF_{peak2}	1.28 ± 0.67	1.47 ± 0.56	− 0.19 ± 0.88	0.482
VLF_{peak}	0.78 ± 0.28	1.01 ± 0.31	− 0.24 ± 0.42	0.077
VMF_{peak}	0.26 ± 0.06	0.32 ± 0.08	− 0.06 ± 0.10	0.042*
KFF_{peak}	2.44 ± 0.55	3.54 ± 1.31	− 1.10 ± 1.43	0.016*
BFF_{peak}	0.15 ± 0.07	0.24 ± 0.17	− 0.09 ± 0.18	0.098
HFF_{peak}	3.43 ± 1.34	4.60 ± 1.50	− 1.17 ± 2.01	0.067
ILF_{peak}	0.96 ± 0.26	1.13 ± 0.15	− 0.17 ± 0.30	0.087
PSF_{peak}	1.02 ± 0.31	1.39 ± 0.29	− 0.37 ± 0.43	0.010*

Values are shown as Mean ± Standard deviation; Muscle forces are reported in Bodyweight (BW).

*Significant differences between PAD and CON.

Δ, differences between PAD and CON; PFF_{peak}, peak plantar flexor force; LGF_{peak}, peak lateral gastrocnemius force; MGF_{peak}, peak medial gastrocnemius force; $SolF_{peak}$, peak soleus force; KEF_{peak1}, peak knee extensor force during weight acceptance; KEF_{peak2}, peak knee extensor force during late stance; VLF_{peak}, peak vastus lateralis force; VMF_{peak}, peak vastus medialis force; KFF_{peak}, peak knee flexor force; BFF_{peak}, peak bicep femoris (short head) force; HFF_{peak}, peak hip flexor force; ILF_{peak}, peak iliacus force; PSF_{peak}, peak psoas force.

3.4. Knee extensors

The peak knee extensor force during weight acceptance, KEF_{peak1}, was lower in patients with PAD compared to controls; however, peak knee extensor force in late stance, KEF_{peak2}, was not different between groups (KEF_{peak1}: Δ = - 0.35 ± 0.41 BW, p = 0.009; KEF_{peak2}: Δ = - 0.19 ± 0.88 BW, p = 0.482; Fig. 3A, Table 2). There was no difference in peak vastus lateralis force, VLF_{peak}; but peak vastus medialis force, VMF_{peak}, was lower in patients with PAD (VLF_{peak}: Δ = - 0.24 ± 0.42 BW, p = 0.077; VMF_{peak}: Δ = - 0.06 ± 0.10 BW, p = 0.042; Fig. 3B & 3C, Table 2).

Both minimum knee extensor power, KEP_{min}, and peak knee extensor power, KEP_{peak}, were not different between patients with PAD and controls (KEP_{min}: Δ = 0.39 ± 0.62 W/kg, p = 0.051; KEP_{peak}: Δ = − 0.15 ± 0.25 W/kg, p = 0.057; Fig. 3D, Table 3). However, minimum power was higher in both vastus lateralis, VLP_{min}, and vastus medialis, VMP_{min}, in patients with PAD, whereas peak power was lower in both vastus lateralis, VLP_{peak}, and vastus medialis, VMP_{peak} in patients with PAD (VLP_{min}: Δ = 0.25 ± 0.34 W/kg, p = 0.021; VMP_{min}: Δ = 0.07 ± 0.10 W/kg, p = 0.026; VLP_{peak}: Δ = − 0.15 ± 0.18 W/kg, p = 0.010; VMP_{peak}: Δ = − 0.04 ± 0.04 W/kg, p = 0.005; Fig. 3E & 3F, Table 3).

Table 3. Group means for peak and minimum muscle powers for patients with peripheral artery disease (PAD) and healthy older controls (CON) groups.

Power (W/Kg)	PAD	CON	Δ = (PAD – CON)	*p*-value
PFP_{min}	− 0.73 ± 0.18	− 0.83 ± 0.21	0.11 ± 0.28	0.209
PFP_{peak}	3.25 ± 1.02	4.41 ± 1.39	− 1.15 ± 1.73	0.036*
LGP_{min}	− 0.11 ± 0.04	− 0.16 ± 0.04	0.05 ± 0.06	0.012*
LGP_{peak}	0.44 ± 0.21	0.71 ± 0.55	− 0.27 ± 0.59	0.132
MGP_{min}	− 0.39 ± 0.15	− 0.52 ± 0.14	0.12 ± 0.20	0.057
MGP_{peak}	1.18 ± 0.23	2.10 ± 1.27	− 0.92 ± 1.29	0.022*
$SolP_{min}$	− 0.29 ± 0.19	− 0.18 ± 0.14	− 0.10 ± 0.23	0.167
$SolP_{peak}$	1.71 ± 0.85	2.04 ± 0.68	− 0.33 ± 1.09	0.333
KEP_{min}	− 1.21 ± 0.47	− 1.60 ± 0.40	0.39 ± 0.62	0.051
KEP_{peak}	0.02 ± 0.16	0.17 ± 0.20	− 0.15 ± 0.25	0.057
VLP_{min}	− 0.38 ± 0.21	− 0.63 ± 0.26	0.25 ± 0.34	0.021*
VLP_{peak}	0.14 ± 0.06	0.28 ± 0.17	− 0.15 ± 0.18	0.010*
VMP_{min}	− 0.15 ± 0.08	− 0.22 ± 0.06	0.07 ± 0.10	0.026*
VMP_{peak}	0.04 ± 0.01	0.08 ± 0.04	− 0.04 ± 0.04	0.005*
KFP_{min}	− 0.48 ± 0.17	− 0.66 ± 0.18	0.17 ± 0.25	0.031*
KFP_{peak}	1.97 ± 0.49	3.16 ± 2.05	− 1.19 ± 2.11	0.064
BFP_{min}	− 0.01 ± 0.01	− 0.02 ± 0.01	− 0.01 ± 0.14	0.031*
BFP_{peak}	0.12 ± 0.09	0.17 ± 0.12	− 0.04 ± 0.15	0.346
HFP_{min}	− 1.02 ± 0.51	− 1.54 ± 0.78	0.52 ± 0.93	0.076
ILP_{min}	− 0.26 ± 0.16	− 0.32 ± 0.12	0.06 ± 0.20	0.355
PSP_{min}	− 0.14 ± 0.08	− 0.22 ± 0.06	0.08 ± 0.10	0.026*

Values are shown as Mean ± Standard deviation; Muscle powers are reported in Watts/kg (W/kg).

*Significant differences between PAD and CON.

Δ, differences between PAD and CON; PFP_{min}, minimum plantar flexor power; PFP_{peak}, peak plantar flexor power; LGP_{min}, minimum lateral gastrocnemius power; LGP_{peak}, peak lateral gastrocnemius power; MGP_{min}, minimum medial gastrocnemius power; MGP_{peak}, peak medial gastrocnemius power; $SolP_{min}$, minimum soleus power; $SolP_{peak}$, peak soleus power; KEP_{min}, minimum knee extensor power; KEP_{peak}, peak knee extensor power; VLP_{min}, minimum vastus lateralis power; VLP_{peak}, peak vastus lateralis power; VMP_{min}, minimum vastus medialis power; VMP_{peak}, peak vastus medialis power; KFP_{min}, minimum knee flexor power; KFP_{peak}, peak knee flexor power; BFP_{min}, minimum bicep femoris (short head) power; BFP_{peak}, peak bicep femoris (short head) power; HFP_{min}, minimum hip flexor power; ILP_{min}, minimum iliacus power; PSP_{min}, minimum psoas power.

3.5. Knee flexors

Although peak knee flexor force, KFF_{peak}, was lower in patients with PAD compared to controls, peak bicep femoris (short head) force, BFF_{peak}, was not different between groups (KFF_{peak}: Δ = - 1.10 ± 1.43 BW, $p = 0.016$; BFF_{peak}: Δ = - 0.09 ± 0.18 BW, $p = 0.098$; Fig. 4A & 4D, Table 2).

Minimum knee flexor power, KFP_{min}, was higher in patients with PAD compared to controls, whereas no significant difference was observed in peak knee flexor power, KFP_{peak} (KFP_{min}: Δ = 0.17 ± 0.25 W/kg, p = 0.031; KFP_{peak}: Δ = - 1.19 ± 2.11, p = 0.064; Fig. 4E, Table 3). Like knee flexor power, minimum bicep femoris (short head) power, BFP_{min}, was higher in patients with PAD and peak bicep femoris (short head) power, BFP_{peak}, was not different between groups (BFP_{min}: Δ = - 0.01 ± 0.14 W/kg, p = 0.031; BFP_{peak}: Δ = - 0.04 ± 0.15 W/kg, p = 0.346; Fig. 4H, Table 3).

3.6. Hip flexors

Peak hip flexor force, HFF_{peak}, was not different between patients with PAD and controls (Δ = - 1.17 ± 2.01 BW, p = 0.067; Fig. 5A, Table 2). Furthermore, peak iliacus force, ILF_{peak}, was not different between groups; however, peak psoas force, PSF_{peak}, was lower in pa- tients with PAD (ILF_{peak}: Δ = - 0.17 ± 0.30 BW, p = 0.087; PSF_{peak}: Δ= - 0.37 ± 0.43 BW, p = 0.010; Fig. 5B & 5C, Table 2).

There were no significant differences in minimum hip flexor power, HFP_{min}, and minimum iliacus power, ILP_{min}, between patients with PAD and controls (HFP_{min}: Δ = 0.52 ± 0.93 W/kg, p = 0.076; ILP_{min}: Δ = 0.06 ± 0.20 W/kg, p = 0.355; Fig. 5D & 5E, Table 3). However, minimum psoas power, PSP_{min}, was higher in patients with PAD compared to controls (Δ = 0.08 ± 0.10 W/kg, p = 0.026; Fig. 5F, Table 3)

3.7. Muscle energy expenditure

Peak metabolic rate during early stance, MR_{peak1}, and peak metabolic rate, MR_{peak2}, during late stance were not different between groups (MR_{peak1}: Δ = 1.16 ± 5.35 W/kg, p = 0.394; MR_{peak2}: Δ = - 0.03 ± 4.56 W/kg, p = 0.981; Fig. 6, Table 4). Similarly, there was no difference in total energy expenditure, TEE (Δ = - 0.08 ± 1.15 J/kg, p = 0.820, Table 4).

Table 4. Group means for muscle energy expenditure parameters for patients with peripheral artery disease (PAD) and healthy older controls (CON) groups.

Metabolic	**PAD**	**CON**	**Δ (PAD – CON)**	***p*-value**
MR_{peak1} (W/Kg)	13.64 ± 5.08	12.48 ± 1.67	1.16 ± 5.35	0.394
MR_{peak2} (W/Kg)	12.03 ± 3.55	12.06 ± 2.85	− 0.03 ± 4.56	0.981
TEE (J/Kg)	5.01 ± 0.92	5.09 ± 0.69	− 0.08 ± 1.15	0.820

Values are shown as Mean ± Standard deviation.

Δ, differences between PAD and CON.

MR_{peak1}, peak metabolic rate during early stance; MR_{peak2}, peak metabolic rate during late stance; TEE, total energy expenditure.

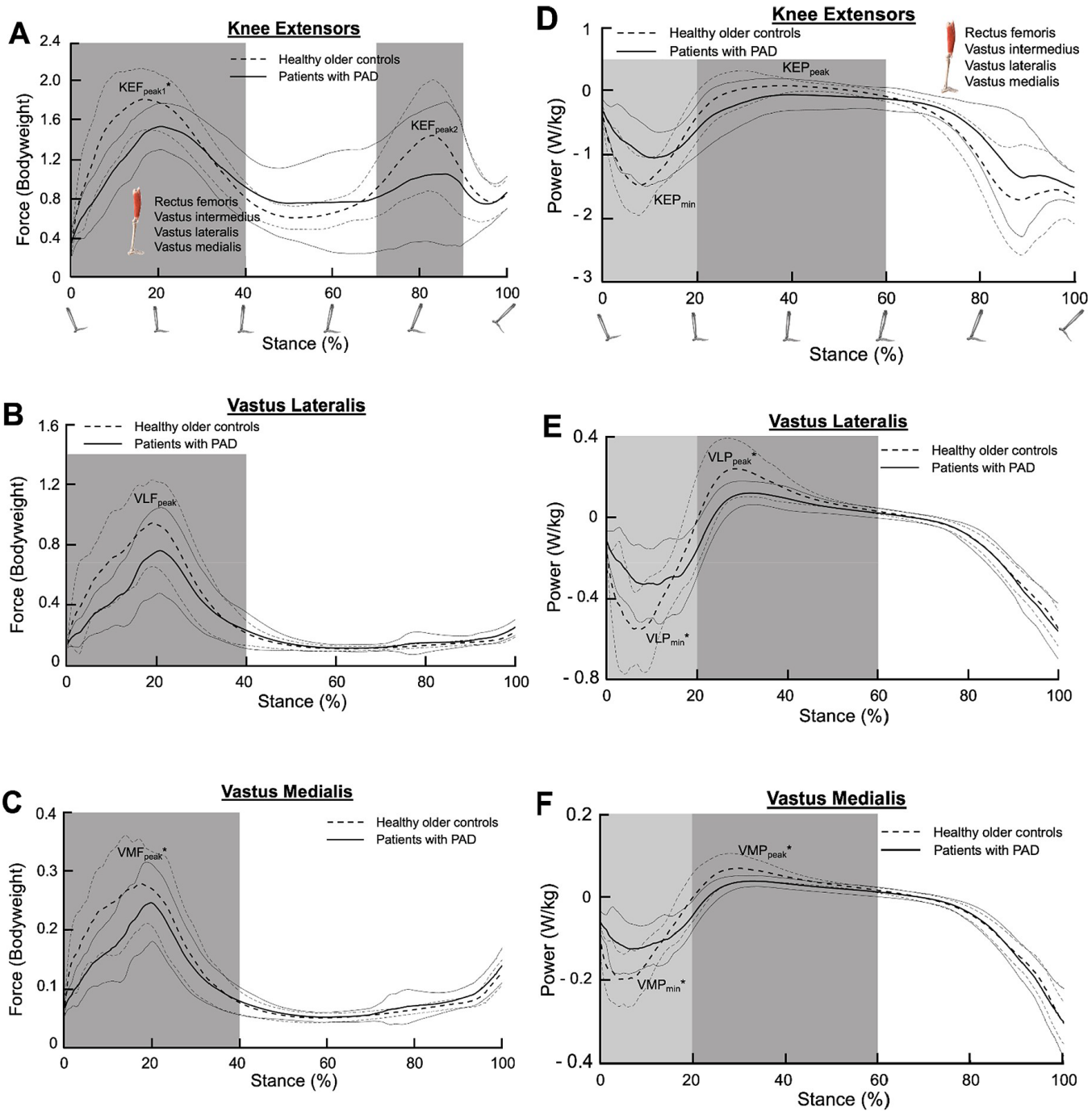

Fig. 3. Muscle forces for A) combined knee extensors, B) vastus lateralis, and C) vastus medialis during stance phase. Figures D), E), and F) represent the muscle power for combined knee extensors, vastus lateralis, and vastus medialis, respectively during stance phase. The dark solid line and the dark dotted line represent the average muscle force/power for patients with peripheral artery disease (PAD) and healthy older controls, respectively. The grey solid lines and the grey dotted lines represent one standard deviation from the average values. The dark grey shaded regions are time ranges where a local maximum (peak) was selected, and the light grey regions are time ranges where a local minimum was selected. Local extrema were selected manually for each subject and compiled for statistical analysis. * indicates a significant difference between patients with PAD and healthy older controls ($p < 0.05$). KEF_{peak1}, peak knee extensor force during weight acceptance; KEF_{peak2}, peak knee extensor force during late stance; VLF_{peak}, peak vastus lateralis force; VMF_{peak}, peak vastus medialis force; KEP_{min}, minimum knee extensor power; KEP_{peak}, peak knee extensor power; VLP_{min}, minimum vastus lateralis power; VLP_{peak}, peak vastus lateralis power; VMP_{min}, minimum vastus medialis power; VMP_{peak}, peak vastus medialis power.

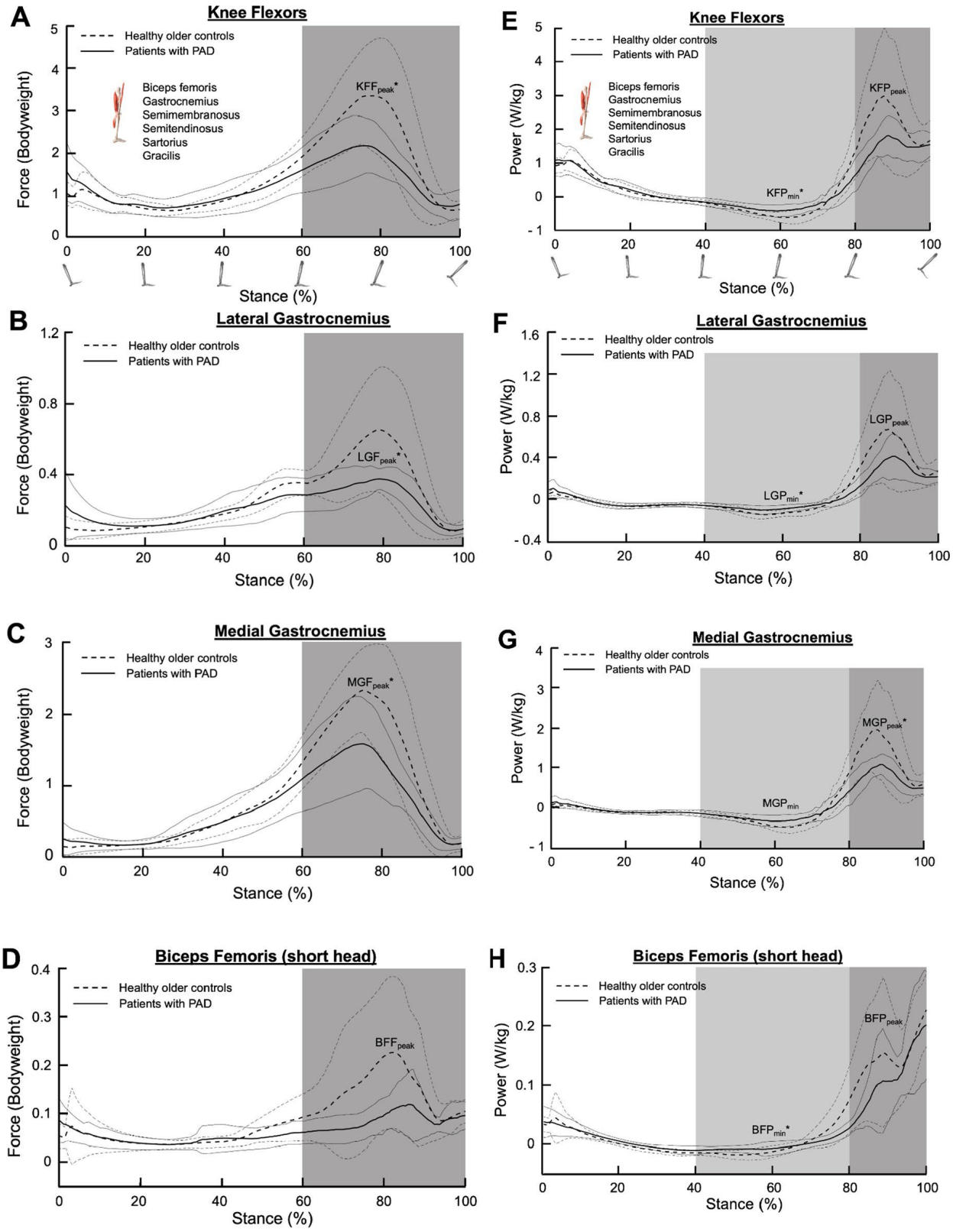

Fig. 4. Muscle forces for A) combined knee flexors, B) lateral gastrocnemius, C) medial gastrocnemius, and D) biceps femoris short head during stance phase. Figures E), F), G), and H) represent the muscle power for combined knee flexors, lateral gastrocnemius, medial gastrocnemius, and biceps femoris short head, respectively during stance phase. The dark solid line and the dark dotted line represent the average muscle force/power for patients with peripheral artery disease (PAD) and healthy older controls respectively. The grey solid lines and the grey dotted lines represent one standard deviation from the average values. The dark grey shaded regions are time ranges where a local maximum (peak) was selected, and the light grey regions are time ranges where a local minimum was selected. Local extrema were selected manually for each subject and compiled for statistical analysis. * indicates a significant difference between patients with PAD and healthy older controls ($p < 0.05$). KFF_{peak}, peak knee flexor force; LGF_{peak}, peak lateral gastrocnemius force; MGF_{peak}, peak medial gastrocnemius force; BFF_{peak}, peak bicep femoris (short head) force; KFP_{min}, minimum knee flexor power; KFP_{peak}, peak knee flexor power; LGP_{min}, minimum lateral gastrocnemius power; LGP_{peak}, peak lateral gastrocnemius power; MGP_{min}, minimum medial gastrocnemius power; MGP_{peak}, peak medial gastrocnemius power; BFP_{min}, minimum bicep femoris (short head) power; BFP_{peak}, peak bicep femoris (short head) power.

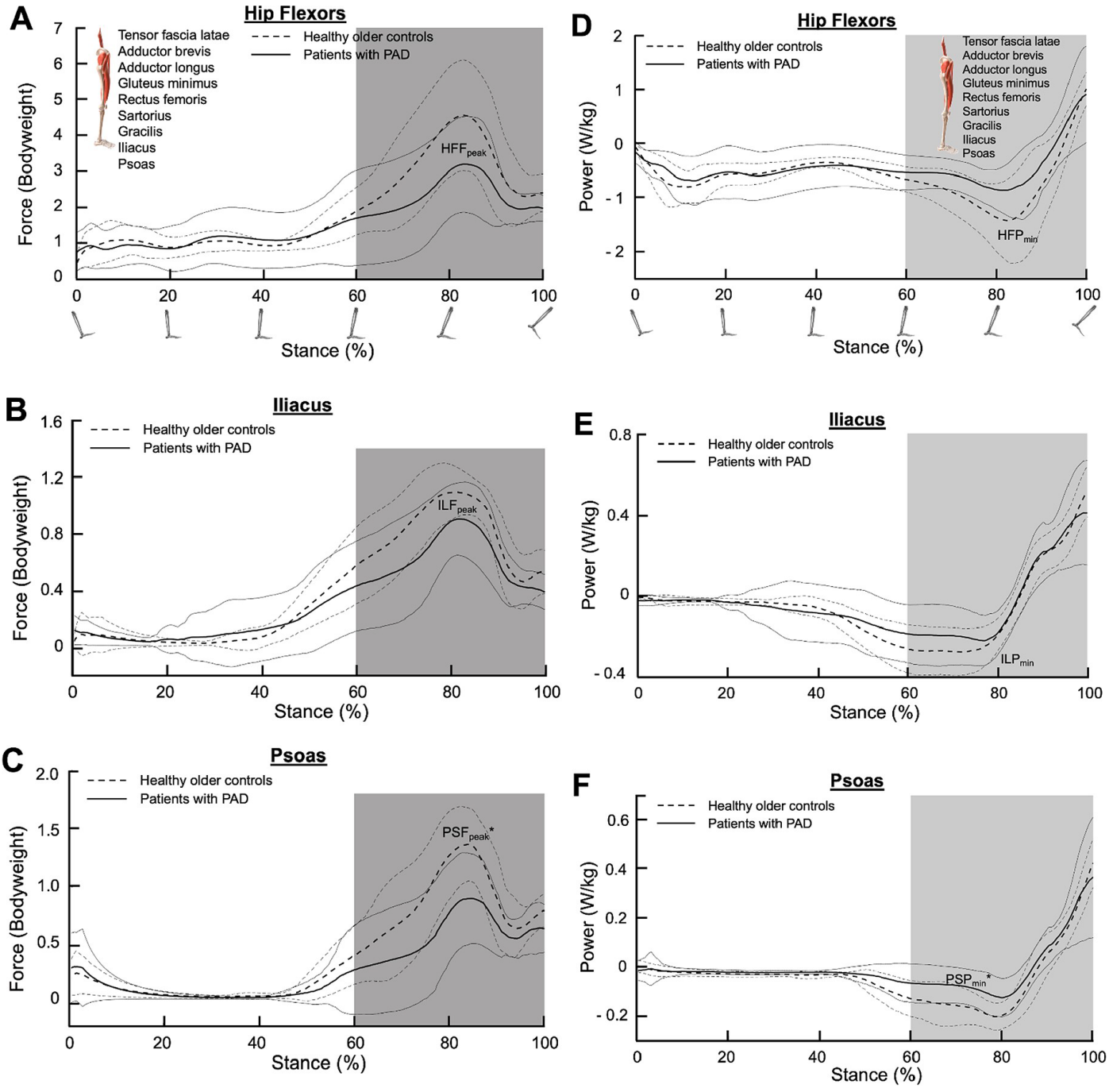

Fig. 5. Muscle forces for A) combined hip flexors, B) iliacus, and C) psoas during stance phase. Figures D), E), and F) represent the muscle power for combined hip flexors, iliacus, and psoas, respectively during stance phase. The dark solid line and the dark dotted line represent the average muscle force/power for patients with peripheral artery disease (PAD) and healthy older controls respectively. The grey solid lines and the grey dotted lines represent one standard deviation from the average values. The dark grey shaded regions are time ranges where a local maximum was selected, and the light grey regions are time ranges where a local minimum was selected. Local extrema were selected manually for each subject and compiled for statistical analysis. * indicates a significant difference between patients with PAD and healthy older controls ($p < 0.05$). HFF_{peak}, peak hip flexor force; ILF_{peak}, peak iliacus force; PSF_{peak}, peak psoas force. HFP_{min}, minimum hip flexor power; ILP_{min}, minimum iliacus power; PSP_{min}, minimum psoas power.

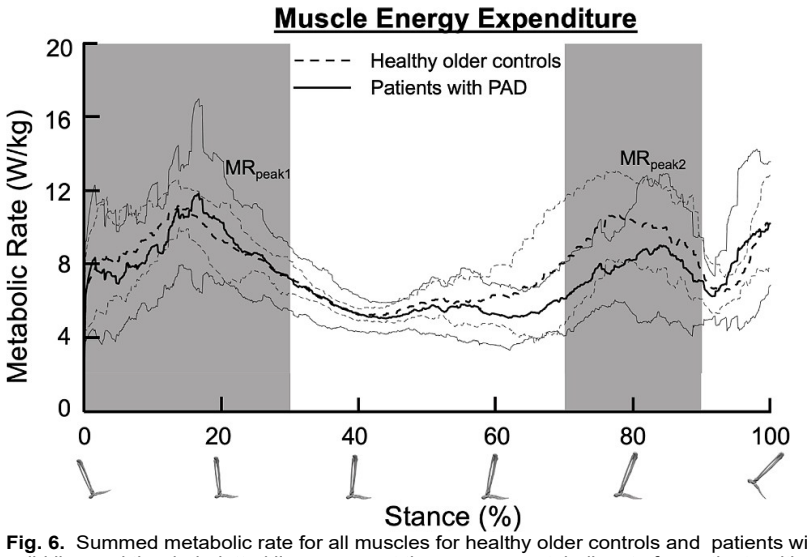

Fig. 6. Summed metabolic rate for all muscles for healthy older controls and patients with peripheral artery disease (PAD) during stance phase. The dark solid line and the dark dotted line represent the average metabolic rate for patients with PAD and healthy older controls respectively. The grey solid lines and the grey dotted lines represent one standard deviation from the average values. MR_{peak1}, peak metabolic rate during early stance; MR_{peak2}, peak metabolic rate during late stance

4.Discussion

The purpose of this study was to use simulations to investigate lower extremity muscle functions in patients with PAD compared to healthy older controls during walking. To the best of our knowledge, this is the first study to perform musculoskeletal modeling and simulation with the OpenSim software in patients with PAD. Our results demonstrate that force and power generation patterns are altered in patients with PAD compared to age-matched controls. Additionally, our results support previous findings that patients with PAD walk at a slower velocity than healthy controls (Kakihana et al., 2017; Koutakis et al., 2010a; McCamley et al., 2019).

Our results show that patients with PAD had attenuated peak energy absorption during weight acceptance in the vastus medialis and lateralis muscles compared to healthy older controls (Fig. 3E & 3F), and the reduced energy absorption in these muscles seems to align with the attenuated peak knee extensor force observed during weight acceptance (Fig. 3A & 3C). The weight acceptance (initial energy absorption) phase on the knee extensor power graphs (Fig. 3D, 3E, & 3F) aligns with the early stance region on traditional knee joint power graphs, which is a region that is attenuated in patients with PAD (Kakihana et al., 2017; Koutakis et al., 2010a; Wurdeman et al., 2012).

According to Neptune's model of mechanical work, the weight acceptance phase of stance is characterized by negative work being performed on the center of mass (Neptune et al., 2004; Tesio and Rota, 2019), and this negative work must be performed by the muscles, since gravity performs positive work on the center of mass during weight acceptance. Our results show that the knee extensors contribute to the negative work performed on the center of mass, as indicated by the negative power contributed by these muscles during weight acceptance (Fig. 3D, 3E, & 3F). Furthermore, it has been demonstrated that walking velocity and work on the center of mass are positively associated; indicating that faster walking velocities align with greater work being done on the center of mass (Adamczyk and Kuo, 2009). Therefore, the attenuated peak energy absorption (Fig. 3E & 3F) and peak force generation (Fig. 3A & 3C) in the knee extensors

could be one of the possible reasons for the slower walking velocity in patients with PAD.

Additional alterations to force and power were observed in the psoas muscle (Fig. 5C & 5F) among those with PAD. During the propulsion phase of stance, peak negative power of the psoas muscle was attenuated in patients with PAD (Fig. 5F), which aligns with previous literature demonstrating attenuated energy absorption in the hip during propulsion in PAD (Kakihana et al., 2017). Our findings demonstrate that in addition to reduced energy absorption, the psoas muscle exhibited reduced force production during the propulsion phase of stance (Fig. 5C). Furthermore, our kinematics results show that patients with PAD exhibited attenuated hip extension during propulsion (Fig. 1C), and this feature may be coupled with the reduction in psoas muscle peak force and peak negative power, since these alterations may be related to reduced stretch of the muscle. Future studies should investigate the interactions between slower walking speed, reduced hip extension, and attenuated hip flexor function during walking in patients with PAD.

Our results suggest the plantar flexor muscles as being problematic for the ankle and knee joints during walking in patients with PAD. Regarding the aggregated muscle groups, peak knee flexor force (Fig. 4A), but not peak plantar flexor force (Fig. 2A), was attenuated during late stance, and this was complimented by a reduction in peak plantar flexor power generation during late stance (Fig. 2E). The greatest contributor to the adverse patterns of force and power appeared to be the medial gastrocnemius, which according to our model, contributed a substantial amount to the total force (Fig. 2C & 4C) and power (Fig. 2G & 4G) generated about the ankle and the knee joints. While the medial and lateral gastrocnemius muscles both demonstrated attenuations in peak force (Fig. 2B, 2C, 4B, & 4C), our simulations suggest that soleus function was preserved (Fig. 2D & 2H), which may account for the maintenance of peak plantar flexor force; however, since the soleus is not biarticular at the knee, the preservation of soleus force could not offset the attenuation in peak knee flexor force observed during late stance. Overall, these observations are significant because reduced force generation and energy expulsion from the plantar flexors could results in less positive work performed on the center of mass and a subsequent decrease in walking velocity.

OpenSim also allows for the calculation of a unique metric, instantaneous metabolic rate, which was derived from the Umberger et al. based metabolic probe (Umberger, 2010; Umberger et al., 2003). In our results, the instantaneous metabolic rate during stance generally followed a bimodal curve, with one maximum during early stance, and the other maximum near toe-off (Fig. 6A). Interesting, despite the attenuated forces and powers exhibited in patients with PAD during the early and late phases of stance, neither maximum of the metabolic rate time series was statistically different compared to controls. Furthermore, the integral of the total metabolic rate time series, which represents the cumulative energy expended by the muscles in the model during stance, was not statistically different between patients with PAD and the age- matched controls (Fig. 6B). This indicates that the muscle constellation chosen to emulate PAD walking was less efficient than the constellation chosen to represent the walking of age-matched controls, since patients with PAD walk at a slower velocity than the age-matched controls.

Our results suggest that patients with PAD walk with a slower velocity in conjunction with attenuated muscle forces and powers contributing to propulsion, which brings the question of which of these factors is dependent on the other. Specifically, is the slower

walking velocity a result of reduced propulsion or is the reduced propulsion a result of selecting a slower walking velocity? While it is true that slower walking velocities are associated with reduced propulsion (Adamczyk and Kuo, 2009), Wurdeman et al. suggests that PAD may contribute to reduced propulsion during late stance, independent of walking velocity (Wurdeman et al., 2012). This suggests that there is something unique about the disease state of PAD which blunts the ability to produce force and power.

In a histological study of medial gastrocnemius muscle tissue, Koutakis et al. observed that PAD preferentially damaged type II (fast twitch) muscle fibers over type I (slow twitch) muscle fibers (Koutakis et al., 2014). Koutakis et al. suggested a shift in fiber type concentration in the PAD muscle from more fast-twitch to more slow-twitch, which matches the patterns of sarcopenia in aging (Koutakis et al., 2014). This observation is intriguing from a biomechanics perspective because it may elucidate the gait alterations that are unique to PAD. Since the mechanical characteristics of slow- and fast-twitch fibers are unique (Powers and Howley, 2018), it would be expected to observe subtle peculiarities in PAD gait characteristics if the hypothesis of a fiber-type shift is valid.

Our modeling results support the hypothesis of a fiber-type shift in the muscles of patients with PAD. The energy systems and anatomy of type II fibers make them optimal for producing power, whereas the energy systems and anatomy of type I fibers make them optimal for resisting fatigue (Powers and Howley, 2018). In our simulation results, the plantar flexor muscles exhibited attenuated force and power generation compared to healthy older controls (Fig. 2E & 2G). Specifically, the medial and lateral gastrocnemius demonstrated attenuated force during late stance (Fig. 2B & 2C), and the medial gastrocnemius was the greatest contributor to the attenuated power at toe off (Fig. 2G), whereas soleus force and power were mostly unaffected by PAD (Fig. 2D & 2H). Considering the work of Koutakis et al., this attenuation pattern is interesting because compared to the soleus, the medial and lateral gastrocnemius are both more dominated by type II fibers (Dahmane et al., 2005; Vandervoort and McComas, 1983), thereby providing in- direct evidence supporting the hypothesis of a fiber type shift in patients with PAD.

Understanding how force and power generation are altered in lower extremity muscle groups during walking in patients with PAD can play an important role in developing interventions and designing assistive devices to restore walking in patients with PAD. This knowledge may help to develop treatment plans that target specific muscle groups such as ankle plantar flexors, knee extensors/flexors or hip extensors/flexors. This work lays the foundation for creating interventions and assistive devices that target specific muscle/muscle groups to enable patients with PAD to generate adequate muscle force and power for walking.

The study has several limitations. A potential limitation of this study was that simulations for both healthy older controls and patients with PAD were performed with default muscle properties provided by the OpenSim model (Rajagopal et al., 2016). The muscle characteristics (maximum isometric force, optimal fiber length, maximum fiber shortening velocity, pennation angle at optimal fiber length, and tendon slack length) for the lower extremity muscles in individuals with PAD are unknown in the existing literature. Another limitation is that there was no electromyography (EMG) data to validate the muscle activation patterns. However, the simulated muscle forces and

activation timings are consistent with previously published data for healthy individuals during walking (Alexander and Schwameder, 2016; Besier et al., 2009; Gomes et al., 2017; Kulmala et al., 2020, 2016; Lin et al., 2012). Future studies should be conducted to generate a PAD model with appropriate muscle characteristics, so the muscle mechanics of patients with PAD can be truly replicated. Specifically, length-tension and velocity-force relationships need to be analyzed extensively in PAD to determine how these relationships change as a function of disease progression, so they can be replicated in modeling. Finally, the muscle forces and powers reported in this study were estimated based on the pain free walking condition. Previous studies from our group and others have shown that patients with PAD walk with significant gait dysfunctions before the onset of claudication pain and gait parameters worsen after the onset of claudication pain (Celis et al., 2009; Koutakis et al., 2010a; Pietraszewski et al., 2019). With our current results, we cannot draw any conclusions about the alterations to gait that occur in patients with PAD after the onset of claudication pain, and future investigates should determine how muscle force and power generation are altered when patients start to experience claudication pain.

5.Conclusions

To the best of our knowledge, this study is the first to analyze the muscular responses during walking in patients with PAD using OpenSim simulations. Overall, our results suggest that muscles surrounding the ankle, knee, and hip joints generate inadequate forces and power compared to age-matched healthy older controls. Our findings provide important information about individual muscle contributions during walking and may be used for the development of future rehabilitation protocols that target specific muscle groups in patients with PAD.

CRediT authorship contribution statement

Hafizur Rahman: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Cody Ander- son:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Formal analysis, Data curation. **Iraklis I. Pipinos:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition. **Jason M. Johanning:** Writing – review & editing, Project administration, Investigation, Funding acquisition. **George P. Casale:** Writing – review & editing, Visualization, Supervision, Investigation, Funding acquisition. **Jianghu Dong:** Writing – review & editing, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Holly DeS- piegelaere:** Writing – review & editing, Resources, Project administration, Data curation. **Mahdi Hassan:** Writing – review & editing, Resources, Project administration, Data curation. **Sara A. Myers:** Writing – review & editing, Writing – original draft, Supervision, Re- sources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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