Gastrocnemius muscle architecture and Achilles tendon properties influence walking distance in claudicants with peripheral arterial disease

Authors

Stephanie Louise King, PhD[1,2] Natalie Vanicek, PhD[2,3] Thomas Daniel O'Brien, PhD[1,4]

1. Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, UK

2. Department of Sport, Health and Exercise Science, University of Hull, UK

3. Discipline of Exercise and Sport Science, University of Sydney, Australia

4. School of Sport, Health and Exercise Science, Bangor University, UK

Corresponding author:

Miss Stephanie King

Research Institute for Sport and Exercise Science

Liverpool John Moores University

Tom Reilly Building

Byrom Street

L3 3AF

Email: s.l.king@ljmu.ac.uk

Phone: +44 7976091341

Running title: Gastronemius muscle and Achilles tendon in PAD-IC

No author has a financial relationship with companies discussed in this manuscript or any other conflict of interest.

This is the peer reviewed version of the following article: King, S. L., Vanicek, N. and O'brien, T. D. (2016), Gastrocnemius muscle architecture and achilles tendon properties influence walking distance in claudicants with peripheral arterial disease. Muscle Nerve, 53: 733–741. which has been published in final form at doi:10.1002/mus.24925 . This article may be used for non-commercial purposes in accordance With Wiley Terms and Conditions for self-archiving.

Abstract:

Objectives: The extent to which gastrocnemius muscle and Achilles tendon properties contribute to the impaired walking endurance of claudicants is not known. **Methods**: Ultrasound images quantified muscle architecture of the lateral and medial gastrocnemius (GL and GM) and were combined with dynamometry during plantarflexor contractions to calculate tendon stress, strain, stiffness, the Young modulus, and hysteresis. Key parameters were entered into multiple regression models to explain walking endurance. **Results:** Worse disease severity was significantly associated with longer fascicle: tendon length ratios (GL R = -0.789 and GM R = -0.828) and increased tendon hysteresis (R = -0.740). Walking endurance could be explained by GL and GM pennation angle, maximum tendon force, tendon hysteresis, and disease severity (R^2 = ~0.6). **Conclusions**: Peripheral arterial disease was associated with functionally important changes in muscle and tendon properties, including the utilization of stored elastic energy. Interventions known to target these characteristics should be adopted as a means to improve walking endurance.

Keywords: Efficiency; hysteresis; endurance; intermittent claudication; gastrocnemius

Introduction

Peripheral arterial disease with intermittent claudication (PAD-IC) primarily affects older adults, and prevalence increases with advancing age[1]. The disease can be physically limiting by impacting adversely on individual quality of life, walking endurance, functional ability, and independence[2-4]. The calf muscle is frequently reported as a site of claudication pain,[5] and there is evidence of plantarflexor dysfunction during level walking[6,7]. However, the contribution of musculoskeletal factors, either individually or in combination with one another, to the functional and quality of life limitations associated with PAD-IC are unclear.

The functional properties of muscle depend on overall size and fascicle arrangement[8]. Muscles required to generate large forces develop highly pennate architecture (the angle between fascicles and the muscle's line of action) with short fascicles, while those that require large excursions/high velocity develop long fascicles[9]. Long fascicles relative to tendon length also have the advantage of reduced relative fascicle velocity for any given movement[9] and decreased energy cost for the same mechanical work[10]. Architectural characteristics adapt to chronic loading, unloading, and aging[11]. Those with PAD-IC are typically older individuals[1] who are less physically active than their healthy counterparts[12] and have the added burden of reduced blood supply to working muscles. Consequently, it is expected that the architecture of claudicant muscles may differ from healthy controls, impacting on muscle function and energy requirements.

Muscle work is transmitted to the skeleton by the tendon, which deforms, stretching and recoiling, during movement. Consequently, tendon properties can modulate the outcome of

muscle contraction by impacting muscle length, maximum muscle force production, and the rate of force development[13]. Tendons store elastic energy when stretched, some of which is lost as heat (defined as hysteresis), but the remainder is recovered during recoil to contribute to the next shortening task. This reduces the metabolic energy required from the muscle during shortening (e.g., propulsion in walking), which improves movement efficiency[14].

Tendon properties have been shown to deteriorate with increasing age,[15] and these adverse changes may be linked to reduced blood supply[16]. Given the increasing prevalence of PAD-IC with advancing age[1] combined with disease-induced reductions in blood supply, it is possible that the tendons of claudicants undergo significant deterioration compared to healthy counterparts. The reduced levels of physical activity associated with PAD-IC[3] mean that claudicant tendons may experience further deterioration with disuse[17]. In combination, it seems likely that the tendons of claudicants would be smaller, weaker, and have greater hysteresis (lost elastic energy) than those of healthy individuals.

The purpose of this study was to determine: (1) whether PAD-IC causes *in vivo* alterations in gastrocnemius muscle architecture and the material and mechanical properties of the Achilles tendon and (2) whether these parameters influence walking endurance. This was achieved by: (1) exploring relationships between muscle-tendon characteristics and disease severity [ankle brachial pressure index (ABPI)] and drawing comparisons to a healthy control group of older adults, and (2) multiple regression modelling of muscle-tendon characteristics to explain initial and absolute claudication walking distances. It was hypothesised that PAD-IC would induce changes comparable to disuse and aging: shorter relative fascicle lengths (fascicle:tendon length ratio), reduced pennation angles, tendon stiffness and the Young

modulus, and greater hysteresis and peak strain. Our second hypothesis was that these muscle-tendon parameters would be able to explain a large portion of walking endurance with the aforementioned changes having detrimental effects.

Methods

Participants

Ethical approval was granted by the NHS Research Ethics Committee (REC reference: 11/YH/0335). A total of 22 participants were recruited, consisting of 12 claudicants (7 unilateral and 5 bilateral) and 10 healthy controls (Table 1). Men and women aged 55-80 years and diagnosed with Rutherford Grade 1 chronic limb ischemia[18] with a narrowing of the superficial femoral artery and not currently under any form of treatment nor previously enrolled in an exercise intervention for PAD-IC were recruited via consultant referral from a local outpatient vascular clinic. Healthy older adults were recruited from the local community as a control group. Participants were excluded if they had a severe or acute cardiovascular, musculoskeletal, neurological, or pulmonary illness; a history of stroke, myocardial infarction or life-limiting diseases, such as cancer; a previous hip or knee replacement or observable gait abnormalities.

Experimental protocol

Disease severity was determined according to the ABPI. Systolic blood pressure was measured in the posterior tibial and dorsalis pedis arteries of each leg and the brachial pressure of both arms, separately, using a sphygmomanometer cuff and a hand held Doppler instrument (Parks Medical Electronics Inc, Oregon, USA). ABPI measures for both lower

limbs were taken pre- and post- a standardized exercise protocol performed on a motorized treadmill (5 minutes, 2.5 km/h, 10% incline). Post-exercise ABPI was used to categorize participant limbs and assess disease severity. In accordance with standard protocol, the ABPI for both legs was then calculated as the higher of the 2 leg artery pressures normalized to the higher brachial pressure of the 2 arms[5]. Symptomatic limbs (ABPI <0.9) for all claudicants were then categorized into those with low disease severity (high ABPI, N=7, providing 8 limbs for analysis) and high disease severity (low ABPI, N=7, providing 8 limbs for analysis) groups, by splitting them at the median ABPI (0.59). For the sake of brevity, these groups will be referred to as 'low ABPI' and 'high ABPI' throughout. This threshold does not necessarily reflect a clinically important marker of vascular function but allows an exploration of whether disease severity-induced changes in muscle and tendon properties were detectable between participants within the ABPI range of our sample. The non-claudicating limb of the unilateral patients was subsequently identified to represent the 'asymptomatic-limb' group (N=7, providing 7 limbs for analysis). Control participants also undertook the exercise protocol to determine ABPI values and confirm the absence of disease (N=10, providing 10 limbs for analysis).

Walking endurance

A modified 6-minute walk test on level ground was performed and was combined with the ACSM claudication pain rating scale[19] to allow those who were able to walk longer than 6-minutes to do so[20]. Patients walked continuously along a 10m walkway at a self-selected pace and reported the level and position of any pain every 20m. Initial claudication distance (ICD) was classed as level 1 on the pain scale and signified the onset of pain. Absolute claudication distance (ACD) was classed as level 4 on the pain scale and signified maximal pain.

Muscle architecture measures

Participants lay prone on a plinth with their ankle plantarflexed and supported on the bed with the musculature relaxed. B-mode ultrasound imaging (50-mm probe length, MyLab50 x-vision, Esaote Biomedica, Genoa, Italy) was used to visualize resting muscle architecture of the GL and GM in the sagittal plane at 50% of muscle length. Fascicle length, pennation angle, and muscle thickness were measured from 3 separately exported images using ImageJ (version 1.44, NIH, USA), with the average taken forward for further analysis. For each image, the length of 1 fascicle with its insertion angle onto the deep aponeurosis and 1 instance of muscle thickness were measured. In cases where the fascicle length exceeded the ultrasound viewing window, the aponeurosis was extrapolated to allow for fascicle length measurements to be estimated[21].

Ultrasound imaging was also used to identify the proximal and distal ends of the muscle, and the calcaneal insertion of the Achilles tendon. A tape measure was then used to measure muscle-tendon unit (MTU) and muscle lengths. Data were analyzed in absolute terms and after scaling to individual anthropometric dimensions.

Measures and calculations for tendon properties

Calculating Achilles tendon force

The gastrocnemius contribution to Achilles tendon force during isometric plantarflexion maximal voluntary contractions (MVCs) was calculated using equations (1) and (2):

1) $AT\ force\ = \frac{GS\ moment}{MA}$

where AT force is Achilles tendon force, GS moment is the gastrocnemius contribution to joint moment, calculated through equation (2), and MA is Achilles tendon moment arm length.

2) $GS\ moment\ =\ joint\ moment\ +\ antagonist\ moment\ -\ soleus\ moment$

where each component is detailed below.

Joint moment was recorded while participants performed 3 ramped plantarflexion MVCs lasting approximately 5 seconds and then returned to rest across the same time period on an isokinetic dynamometer (Biodex System 3, Biodex Medical Systems Inc, New York, USA). Participants were seated in a standardized upright position: hip flexed (85°), knee extended (0°), and ankle dorsiflexed (maximum dorsiflexion within individual range of motion). Practice trials were performed prior to testing, and visual feedback was provided to ensure a consistent rate of rise in plantarflexor moment during each test. Adequate rest was provided between trials (~1 min), and the trial with the highest MVC was selected for further analysis.

Antagonist co-activation during the plantarflexion MVC was assessed using surface EMG of the tibialis anterior (Telemyo 2400T, Noraxon, Arizona, USA). The dorsiflexion EMG-moment relationship was constructed from 4 dorsiflexion contractions of increasing intensity. The tibialis anterior EMG at each stage of the ramped plantarflexion trials was then substituted into this relationship to predict antagonist dorsiflexor moment[22]. The soleus contribution to plantarflexor moment was quantified during additional plantarflexion

contractions lasting approximately 3 seconds with the knee flexed to 90°, where the gastrocnemius muscles were slack and did not contribute to the joint moment[23]. The soleus EMG-moment relationship across the 2 joint configurations [knee extended (0°) and knee flexed (90°)] was used to correct activation differences (equation 3):

3) $$Soleus\ moment\ Knee\ 0° = \frac{Soleus\ moment\ Knee\ 90° * Soleus\ EMG\ Knee\ 0°}{Soleus\ EMG\ Knee\ 90°}$$

Achilles tendon moment arm (MA) was calculated using the tendon excursion method[23,24] and ultrasound imaging to quantify linear myotendinous junction displacement.

Achilles tendon dimensions and elongation

For the purposes of calculating tendon properties, Achilles tendon resting length was measured from the proximal origin at the myotendinous junction of medial gastrocnemius to the distal insertion at the calcaneus while the ankle was in maximum dorsiflexion prior to plantarflexion contractions (participant positioning described above). These locations were identified using ultrasound imaging, and the length was measured using a tape. Free tendon cross-sectional area (CSA) was measured at 1, 2, and 3 cm proximal to the insertion onto the calcaneus using axial-plane ultrasound imaging[23] and was analyzed using ImageJ. The average of all 3 sites was used for further calculations.

The ultrasound probe was aligned with the distal myotendinous junction of the medial gastrocnemius and the Achilles tendon in the sagittal plane and was securely fixed to the skin with an echo-absorptive marker within the viewing window to allow for correction of any

artifacts caused by probe movement[25]. Ultrasound videos were synchronized with plantarflexor moments during MVCs lasting approximately 5 seconds (described above) to track myotendinous junction displacement. Images were digitized to measure tendon elongation at each 10% of peak tendon force using ImageJ.

Tendon stiffness, the Young modulus, and tendon hysteresis

Force-elongation curves were constructed for the loading (increasing contraction) and unloading (relaxation) phases for all participants, and each was fitted with a second order polynomial equation between 10-100% of tendon force (for all R^2<.95). The following parameters were calculated for each participant at their individual MVC: tendon stiffness, strain, stress, and the Young modulus. Stiffness was calculated as the gradient of the force-elongation curve by differentiating the equation at each individual's MVC. Tendon strain was calculated by normalizing elongation to resting length. Tendon stress was calculated by normalizing tendon force to CSA. The tendon Young modulus was calculated as tendon stiffness multiplied by the ratio of tendon length to CSA[13,23,26]. Energy stored in the tendon was calculated as the area beneath the whole of the loading curve, and energy released was calculated as the area beneath the unloading curve by integrating a second second order polynomial equation describing the respective force-elongation curves between 0-100% of tendon force. Hysteresis was calculated as the difference between the energy stored and energy released and normalized as a percentage of the energy stored.

Statistical analysis

A Pearson partial product-moment correlation was performed to assess relationships between disease severity (as assessed by ABPI and controlled for the influence of age), walking endurance (as assessed by ICD and ACD), and gastrocnemius architecture parameters and all Achilles tendon parameters in the symptomatic limbs only. Data were examined for normal distribution and outliers by visual inspection of histogram and box-plots. A one-way ANOVA was performed to compare differences in muscle-tendon parameters between the healthy controls, asymptomatic-limb group, and high and low ABPI groups. Sidak *post-hoc* tests were applied when appropriate. Where non-parametric variables were identified, independent samples Kruskal-Wallis tests were performed with subsequent Mann-Whitney *U* tests applied where appropriate.

To assess which architectural parameters and Achilles tendon properties were most important to explain variations in walking endurance (as measured by ICD and ACD), a backwards step-wise regression was performed on the symptomatic limbs (N=16) to avoid the suppressor effect typically associated with forwards step-wise regression models[27]. Key variables included in the analysis were GL and GM fascicle:tendon lengths, pennation angle and muscle thickness; tendon force, strain, stiffness, and mechanical hysteresis; and ABPI.

For all statistical tests, significance was accepted at $P \leq .05$, and trends were accepted at $P < .10$. Where appropriate, effect size (*ES*) and study power is also stated. For correlation and regression analyses, a moderate relationship was accepted as R=.40 – .59, a strong relationship as R=.60 – .79, and a very strong relationship as R=.80 – 1.0[28]. Since low ABPI values indicate high disease severity, a positive relationship signifies a decrease in the respective parameter with increasing disease severity.

Results

No significant differences were found between any groups for age (P=0.414), height (P=0.345), mass (P=0.543), or BMI (P=0.796) (Table 1). No significant differences existed between low ABPI, high ABPI, or unilateral (asymptomatic-limb) groups in ICD (P=0.197) or ACD (p=.321). Between-group differences in ABPI were consistent with disease presentation.

Correlation analysis

Increasing disease severity was significantly correlated with longer GL and GM fascicle: tendon lengths, shorter tendons, greater tendon strain, and greater tendon hysteresis (Figure 1). Poorer walking endurance, as measured by ICD, was associated with longer GL and GM fascicle: tendon lengths, greater GM pennation angle, and trends towards higher tendon strain and hysteresis. Poorer maximum walking endurance, as measured by ACD, was associated with increased GL and GM pennation angle. Individual R- and P-values are listed in Tables 2 and 3 for all correlations. Disease severity was not associated with ICD (R = 0.215, P = 0.441) or ACD (R = 0.161, P = 0.566).

Between-group comparisons

Several differences were detected between groups in absolute and relative muscle-tendon dimensions (Table 4). In the GL, relative fascicle: tendon length was smaller in the high ABPI group compared to the control group (P = 0.027, ES = 0.37, power = 0.40). In the GM,

the low ABPI (high disease severity) group had longer fascicle lengths compared to controls (P = 0.014, ES = 0.55, power = 0.78) and longer fascicle: tendon lengths compared to the high ABPI group (P = 0.050, ES = 0.56, power = 0.29).

At individual maximum tendon force, both claudicant groups and the asymptomatic-limb group demonstrated reduced Young modulus compared to the control group (P = 0.029 - 0.100, ES = 0.41 - 0.47, power = 0.50 - 0.65; Table 4). Compared to controls, tendon stiffness was lower in the asymptomatic-limb group (P = 0.053, ES = 0.57, power = 0.85; Table 5). The low ABPI (high disease severity) had significantly greater mechanical hysteresis compared to the high ABPI group (P = 0.004, ES = 0.62, power = 0.88) and showed a trend towards increased hysteresis compared to the control group (42%, P = 0.065, ES = 0.49, power = 0.65) (Table 5).

No significant differences existed between all groups for MVC (P = 0.631), GS moment (P = 0.738), moment arm (P = 0.414), or peak tendon force (P = 0.825) (Table 5).

Regression analysis

Walking distances were not explained by ABPI alone (see correlations above). The inclusion of muscle-tendon parameters with ABPI led to significant predictions of both ICD and ACD (P = 0.041 and P = 0.037, respectively). Sixty-five percent of the variance in ICD could be explained using ABPI, GL and GM pennation angle, tendon force, tendon stiffness, and mechanical hysteresis (Table 6). Similarly, ABPI, GL and GM pennation angle, tendon force,

and mechanical hysteresis was the strongest combination to predict ACD and could explain 59% of the variance (Table 7).

Discussion

This study quantified the fascicle architecture of the gastrocnemii muscles and the mechanical and material properties of the Achilles tendon in patients with PAD-IC. In partial support of our first hypothesis, associations were found between low ABPI values (increased disease severity), relatively longer GL and GM fascicles, and increased tendon mechanical hysteresis. These were supported by significant differences between claudicants, particularly those with more severe forms of disease, and controls in both architectural parameters and tendon properties. The results indicate that these changes in muscle-tendon properties play an important role in influencing walking endurance in claudicants and can explain a large portion of the variance in walking distances that ABPI alone cannot.

Correlation analysis revealed that both GL and GM fascicle lengths increased while tendon length decreased significantly, leading to greater fascicle: tendon length ratios with increasing disease severity. Additionally, those with lower ABPI had significantly longer GM fascicle: tendon lengths compared to those with higher ABPI (Table 2). These adaptations allow the muscle-tendon unit to lengthen and shorten with less relative fascicle, and therefore sarcomere, displacement. As a result, the GM MTU in those with low ABPI values appear to have adapted in such a way that would facilitate length changes during movement with less energy consumption per unit of muscle force[10]. However, the impact of this potential energy saving adaptation may be negated by the concomitant increase in mechanical hysteresis,

which was 42% greater in those with low ABPI compared to the control group (Figure 1 and Table 5). Individuals with more severe forms of PAD-IC and those with limited walking endurance are less able to utilize this energy recovery mechanism in the tendon and must provide metabolic energy to the muscles to make up the shortfall, thus increasing the energy cost of movement. This observation is commensurate with reported reductions in walking economy with greater disease severity[29]. Therefore, efforts to improve the recovery and utilization of the energy stored in the tendon (by reducing hysteresis) through appropriately designed interventions, such as progressive resistance training[26], may have substantial benefits for walking endurance in this population.

The second aim of this study was to elucidate the extent to which gastrocnemius muscle architecture and Achilles tendon properties influence walking endurance. ABPI alone could not explain variations in walking distances, but when combined with the muscle-tendon parameters, significant models that could explain a moderate-large portion of the variance (R^2 = 0.65 and R^2 = 0.59 for ICD and ACD, respectively) were found. The construct of both models with the highest adjusted R^2 (Tables 6 and 7) has justifiable biomechanical and physiological reasoning, and this provides confidence in their validity. We hypothesized that greater hysteresis would have a negative impact on walking endurance, which has been substantiated. Pennation angle, which was included in both models, can be considered to be an index of muscle functional "design", with lower angles suited to large excursions rather than force production[9]. Since pennation angle was predominantly associated with negative coefficients in both models containing the fewest parameters and those with the highest adjusted R^2 (Tables 6 and 7), this suggests that muscles with a "design" favouring length changes are beneficial to walking endurance. Longer fascicle: tendon length ratios would also reflect such a functional design, thus, the exclusion of fascicle: tendon length ratio from the

models suggests that pennation angle was adequate to explain this portion of the variance. Interestingly, GM pennation with negative coefficients was present in models that could explain the most variance and the most efficient models for both ICD and ACD, reinforcing the importance of muscle "design" in predicting walking capacity. Finally, tendon force had a positive coefficient in both models, indicating that greater muscle strength allowed longer walking distances. This may be because greater maximum strength would mean the mechanical demands of walking are lower relative to maximum capacity, thus according to the size principle[30], the muscle may rely to a greater extent on the more efficient slow-type muscle fibers. It must be acknowledged that the sample size of this study was small for typical multiple regression models, which require further exploration and validation. Future work should further explore the role of each parameter in explaining walking endurance and consider how these variables respond to treatment and the subsequent impact on walking endurance.

Interestingly, the tendon properties in the asymptomatic-limb group were more similar to the claudicating limbs than the controls. This observation was confirmed by additional pairwise *t*-tests between the symptomatic and asymptomatic limbs of unilateral claudicants that revealed no significant differences between limbs. It suggests that either systemic adaptations were impacting the asymptomatic limb, in particular the asymptomatic tendon, or disuse resulting from reduced physical activity levels led to deterioration in tendon properties. At this stage it is not possible to determine which of these mechanisms may be responsible.

This study has some limitations. First, architectural characteristics were measured at a single site within the muscle, and muscle architecture may not be homogeneous across the entire

muscle. Second, the calculation of tendon force required simplification of the forces acting about the joint, but this approach has been validated in numerous previous studies[13,23,26]. Specifically, accounting for antagonistic co-activation using the EMG of the TA during dorsiflexor contractions likely underestimates the true dorsiflexor co-activation moment[31]. Additionally, we assumed that the gastrocnemii did not contribute towards measured plantarflexor moment with the knee flexed at 90°, though we were unable to confirm this quantitatively. However, it is certain that, at such a short muscle length, the gastrocnemius force was substantially reduced compared to longer muscle lengths. There were no between group differences in antagonist co-activation, moment-angle relationships[32], or associations with disease severity, therefore we do not believe these assumptions have a confounding effect on our data. It must also be acknowledged that our sample was small, which may have caused some Type II error. Nonetheless, disease-associated changes were detected, and biomechanically and physiologically sound multiple regression models were established, thus the sample appeared adequate for the purposes of the study. Future work should seek to validate these models in larger and more diverse samples.

This study indicates that improving tendon properties and increasing strength, but without increasing pennation angle, would be beneficial for walking endurance. Finding such an intervention is not simple, since the majority of exercise interventions that improve strength, e.g. resistance training, also increase pennation angle[33]. However, eccentric resistance training may provide a viable solution, since it has been shown to improve tendon properties[34] and increase muscle strength while lengthening fascicles but not increasing pennation[33]. Previous research on resistance training with claudicants is sparse, with conflicting reports of effectiveness[35]. This inconsistency could be due to the use of conventional, predominantly concentric resistance training, which may not elicit the optimal

adaptations for walking endurance. Future exercise studies should evaluate the effectiveness of eccentric resistance training for improving walking endurance of individuals with PAD-IC.

Conclusions

This study has shown that more severe forms of PAD-IC is associated with muscle remodelling towards larger GM fascicle: tendon length ratios and less effective utilization of elastic energy stored in the Achilles tendon (increased hysteresis). Importantly, when combined with ABPI, tendon hysteresis, architectural parameters of muscle functional design, and the muscle's force producing capacity were able to explain large portions (~65%) of walking endurance. These findings suggest that eccentric resistance training of the plantarflexor muscles may be a valuable intervention to improve tendon properties, muscle function, and ultimately walking endurance.

Abbreviations:

ABPI – Ankle brachial pressure index

ACD – Absolute claudication distance

BMI – Body mass index

CSA – Cross-sectional area

ES – Effect size

GL – Lateral gastrocnemius

GM – Medial gastrocnemius

GS – Gastrocnemii (i.e. lateral and medial gastrocnemius combined)

ICD – Initial claudication distance

MTU – Muscle-tendon unit

MVC – Maximal voluntary contraction

PAD-IC – Peripheral arterial disease

TA – Tibialis anterior

References

1. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18-e209.

2. Spronk S, White JV, Bosch JL, Hunink MG. Impact of claudication and its treatment on quality of life. Semin Vasc Surg. 2007;20(1):3-9.

3. McDermott MM, Greenland P, Liu K, Guralnik J, Criqui MH, Dolan NC, et al. Leg Symptoms in peripheral arterial disease. Associated clinical characteristics and functional impairment. JAMA. 2001;286(13):1599-606.

4. Chetter IC, Spark JI, Dolan P, Scott DJA, Kester RC. Quality of Life Analysis in Patients with Lower Limb Ischaemia: Suggestions for European Standardisation. Eur J Vasc Endovasc. 1997;13:597-604.

5. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc. 2007;33 Suppl 1:S1-75.

6. Wurdeman SR, Koutakis P, Myers SA, Johanning JM, Pipinos II, Stergiou N. Patients with peripheral arterial disease exhibit reduced joint powers compared to velocity-matched controls. Gait & Posture. 2012;36(3):506-9.

7. Koutakis P, Johanning JM, Haynatzki GR, Myers SA, Stergiou N, Longo GM, et al. Abnormal joint powers before and after the onset of claudication symptoms. J Vasc Surg. 2010;52(2):340-7.

8. Ward SR, Eng CM, Smallwood LH, Lieber RL. Are current measurements of lower extremity muscle architecture accurate? Clinical Orthopaedics and Related Research. 2009;467(4):1074-82.

9. Lieber RL, Friden J. Functional and clinical significance of skeletal muscle architecture. Muscle Nerve. 2000;23:1647-66.

10. Beltman JGM, van der Vliet MR, Sargeant AJ, de Haan A. Metabolic cost of lengthening, isometric and shortening contractions in maximally stimulated rat skeletal muscle. Scandanavian Physiological Society. 2004;182(179-187).

11. Narici MV, Maganaris CN. Plasticity of the muscle-tendon complex with disuse and aging. Exerc Sport Sci Rev. 2007;35(3):126-34.

12. McDermott M, Liu K, Greenland P, Guralnik JM, Criqui MH, Chan C, et al. Functional Decline in PeripheralArterialDisease Associations With the Ankle Brachial Index and Leg Symptoms. JAMA. 2004;292:453-61.

13. Maganaris CN, Paul JB. In vivo human tendon mechanical properties. J Appl Physiol. 1999;521(1):307-13.

14. Peltonen J, Cronin NJ, Stenroth L, Finni T, Avela J. Viscoelastic properties of the Achilles tendon in vivo. Springerplus. 2013;2(1):212.

15. Kubo K, Kanehisa H, Miyatani M, Tachi M, Fukunaga T. Effect of low-load resistance training on the tendon properties in middle-aged and elderly women. Scandanavian Physiological Society. 2003;178:25-32.

16. Del Buono A, Chan O, Maffulli N. Achilles tendon: functional anatomy and novel emerging models of imaging classification. International orthopaedics. 2013;37(4):715-21.

17. Reeves ND, Maganaris CN, Ferretti G, Narici MV. Influence of 90-day simulated microgravity on human tendon mechanical properties and the effect of resistive countermeasures. J Appl Physiol. 2005;98(6):2278-86.

18. Rutherford RB, Baker D, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: Revised version. J Vasc Surg. 1997;26:517-38.

19. Durstine JL, Moore GE. ACSM's Exercise Management in Persons with Chronic Diseases and Disabilities. Leeds: Human Kinetics; 2003.

20. King S, Vanicek N, Mockford KA, Coughlin PA. The effect of a 3-month supervised exercise programme on gait parameters of patients with peripheral arterial disease and intermittent claudication. Clin Biomech. 2012;27(8):845-51.

21. Reeves ND, Narici MV. Behavior of human muscle fascicles during shortening and lengthening contractions in vivo. J Appl Physiol. 2003;95(3):1090-6.

22. Kellis E, Baltzopoulos V. The effects of antagonist moment on the resultant knee joint moment during isokinetic testing of the knee extensors. Europ J Appl Physiol. 1997;76(3):253-9.

23. Maganaris CN, Paul JB. Tensile properties of the in vivo human gastrocnemius tendon. J Biomech. 2002;35:1639-46.

24. Fath F, Blazevich AJ, Waugh CM, Miller SC, Korff T. Direct comparison of in vivo Achilles tendon moment arms obtained from ultrasound and MR scans. J Appl Physiol. 2010;109(6):1644-52.

25. Maganaris CN, Paul JP. Hysteresis measurements in intact human tendon. J Biomech. 2000;33(12):1723-7.

26. Reeves ND, Narici MV, Maganaris CN. Strength training alters the viscoelastic properties of tendons in elderly humans. Muscle Nerve. 2003;28(1):74-81.

27. Menard S. Logistic regression: From introductory to advanced concepts and applications: SAGE, Inc; 2010.

28. Taylor R. Interpretation of the Correlation Coefficient: A Basic Review. Journal of Diagnostic and Medical Sonography. 1990;6(1):35-9.

29. Gardner AW, Ritti-Dias RM, Stoner JA, Montgomery PS, Scott KJ, Blevins SM. Walking economy before and after the onset of claudication pain in patients with peripheral arterial disease. J Vasc Surg. 2010;51(3):628-33.

30. Henneman E, Somjen G, Carpenter DO. Functional significance of cell size in spinal motorneurons. J Neurophysiol. 1965;28(3):560-80.

31. Billot M, Simoneau E, Van Hoecke J, Martin A. Coactivation at the ankle joint is not sufficient to estimate agonist and antagonist mechanical contribution. Muscle Nerve. 2010;41(4):511-8.

32. King S, O'Brien TD, Vanicek N. Isometric and isokinetic strength profiles of claudicants with peripheral arterial disease. Gait & Posture. 2014;39:S29-S30.

33. Reeves ND, Maganaris CN, Longo S, Narici MV. Differential adaptations to eccentric versus conventional resistance training in older humans. Exp Physiol. 2009;94(7):825-33.

34. Malliaras P, Kamal B, Nowell A, Farley T, Dhamu H, Simpson V, et al. Patellar tendon adaptation in relation to load-intensity and contraction type. J Biomech. 2013;46(11):1893-9.

35. Parmenter BJ, Raymond J, Dinnen P, Singh MA. A systematic review of randomized controlled trials: Walking versus alternative exercise prescription as treatment for intermittent claudication. Atherosclerosis. 2011;218(1):1-12.

Figure 1. Correlations between disease severity (ABPI) and GL and GM fascicle : tendon length ratio (a and b respectively) and tendon mechanical hysteresis (c). Average control and asymptomatic-limb groups are shown for comparison and are not included in correlation analysis

Table 1. Participant characteristics. Data are presented as group mean (SD) unless otherwise stated. BMI – Body mass index, ABPI – Ankle brachial pressure index. ICD – Initial claudication distance. ACD – Absolute claudication distance.

	Low ABPI	High ABPI	Asymptomatic-limb	Healthy Control
# limbs	8	8	7	10
% Men	77.8	87.5	57.1	40
Age (years)	64.3 (4.7)	65.5 (8.0)	66.1 (7.5)	61.6 (3.6)
Height (m)	1.72 (0.07)	1.73 (0.06)	1.69 (0.10)	1.67 (0.09)
Mass (Kg)	81.1 (15.9)	82.5 (21.5)	82.3 (21.1)	72.3 (10.9)
BMI (Kg/m^2)	27.6 (5.3)	27.3 (5.9)	28.5 (4.8)	26.1 (3.7)
ABPI pre-exercise	0.71 (0.19)	0.89 (0.22)	1.01 (0.16)	1.00 (0.09)
ABPI post-exercise	0.39 (0.17)	0.63 (0.15)	0.90 (0.06)	1.01 (0.15)
ICD (m)	106.3 (51.0)	123.8 (47.2)	80.0 (16.7)	n/a
ACD (m)	285.0 (141.7)	298.8 (147.0)	195.0 (82.6)	n/a
Disease duration (months)	42.8 (44.2)	52.9 (46.7)	31.9 (44.4)	n/a
% Hypertension	50	50	42.9	10
% Hypercholesterolemia	50	50	71.4	20
% past smokers	50	62.5	57.1	30
% present smokers	50	37.5	42.9	0

Table 2. Pearson partial correlations (controlled for the influence of age) between disease severity (ABPI), walking endurance (ICD and ACD), and gastrocnemius architectural parameters. Values in bold font indicate those reaching significance ($P \leq .05$), and values in italics indicate those demonstrating trends towards significance ($P \leq .10$).

Gastrocnemius architecture		GL fascicle : tendon length	GM fascicle : tendon length	GL fascicle : muscle length	GM fascicle : muscle length
ABPI	Correlation	**-0.789**	**-0.828**	-0.451	-0.267
	Significance	**0.001**	**<0.001**	0.106	0.357
ICD	Correlation	**-0.547**	*-0.487*	-0.312	-0.252
	Significance	**0.043**	*0.081*	0.277	0.385
ACD	Correlation	-0.436	-0.345	-0.290	-0.353
	Significance	0.120	0.228	0.315	0.216
Gastrocnemii architecture		GL pennation	GM pennation		
ABPI	Correlation	0.188	-.332		
	Significance	0.503	.226		
ICD	Correlation	-0.310	**-0.807**		
	Significance	0.261	**<0.001**		
ACD	Correlation	**-0.566**	**-0.803**		
	Significance	**0.028**	**<0.001**		

Table 3. Pearson partial correlations (controlled for the influence of age) between disease severity (ABPI), walking endurance (ICD and ACD), and Achilles tendon properties. Values in bold font indicate those reaching significance ($P \leq .05$) and values in italics indicate those demonstrating trends towards significance ($P \leq .10$).

Achilles tendon properties		Tendon length	Tendon force	Elongation at maximal tendon force	Stiffness at maximal tendon force
ABPI	Correlation	**0.728**	0.052	-0.061	0.166
	Significance	**0.003**	0.854	0.836	0.570
ICD	Correlation	0.365	-0.205	-0.110	-0.141
	Significance	0.199	0.463	0.709	0.630
ACD	Correlation	0.262	0.224	-0.124	0.165
	Significance	0.366	0.423	0.672	0.573

Achilles tendon properties		Young modulus at maximal tendon force	Peak strain	Mechanical Hysteresis
ABPI	Correlation	0.247	*-0.490*	-0.740
	Significance	0.395	*0.075*	0.006
ICD	Correlation	-0.146	-0.261	-0.598
	Significance	0.619	0.367	0.040
ACD	Correlation	0.115	-0.219	-0.277
	Significance	0.696	0.453	0.384

Table 4. Group mean (SD) musculotendinous length and size parameters.

	Low ABPI	High ABPI	Asymptomatic-limb	Control
Tibia length (cm)	40.5 (2.4)	**41.6 (1.3)^{A}**	39.5 (2.5)	38.9 (3.2)
MTU length (cm)	*45.5 (3.7)^{C}*	**45.8 (1.1)^{C}**	43.0 (3.7)	41.6 (4.3)
Achilles tendon length (cm)	22.3 (3.0)	**24.2 (1.1)^{C,A}**	21.5 (2.7)	20.6 (2.5)
Achilles tendon CSA (cm^2)	89.6 (13.1)	98.5 (23.9)	82.5 (19.5)	85.1 (12.4)
Lateral Gastrocnemius				
Muscle length (cm)	22.4 (1.2)	21.3 (0.8)	21.6 (1.8)	20.4 (2.5)
Fascicle length (cm)	4.98 (0.78)	4.77 (0.38)	4.54 (0.50)	4.60 (0.64)
Fascicle length : Muscle length	0.22 (0.03)	0.22 (0.02)	0.21 (0.02)	0.23 (0.04)
Fascicle length : Tendon length	0.23 (0.05)	**0.20 (0.02)^{C}**	0.21 (0.02)	0.22 (0.03)
Thickness (cm)	1.26 (0.23)	1.29 (0.20)	1.24 (0.24)	1.17 (0.21)
Pennation (°)	15.2 (2.0)	16.7 (2.8)	16.9 (2.8)	14.8 (1.8)
Medial Gastrocnemius				
Muscle length (cm)	23.4 (2.6)	22.0 (1.9)	21.3 (2.5)	21.4 (2.5)
Fascicle length (cm)	**4.34 (0.59)^{C}**	4.09 (0.29)	4.10 (0.34)	3.65 (0.45)
Fascicle length : Muscle length	0.19 (0.03)	0.19 (0.02)	0.19 (0.03)	0.17 (0.02)
Fascicle length : Tendon length	**0.20 (0.03)^{H}**	0.17 (0.01)	0.19 (0.03)	0.18 (0.03)
Thickness (cm)	1.77 (0.33)	1.68 (0.31)	1.73 (0.17)	1.62 (0.20)
Pennation (°)	27.5 (4.5)	26.4 (3.8)	27.9 (4.0)	29.4 (3.8)

Values in bold font indicate those reaching significance ($P \leq .05$), and values in italics indicate those demonstrating trends towards significance ($P \leq .10$). L: vs low ABPI group (High disease severity); H: vs high ABPI group (low disease severity); A: vs asymptomatic-limb group; C: vs control group

Table 5. Group mean (SD) measures of MVC, Achilles tendon tensile properties, and measures of elastic energy.

	Low ABPI	**High ABPI**	**Asymptomatic-limb**	**Control**
MVC (Nm)	116.4 (29.0)	100.6 (27.2)	102.2 (33.5)	114.4 (28.5)
GS moment (Nm)	73.6 (20.6)	64.4 (22.6)	63.6 (20.8)	65.2 (14.6)
Moment arm (cm)	3.47 (0.73)	3.40 (0.48)	3.59 (0.67)	3.24 (0.58)
Tendon force (N)	2150.3 (591.0)	1947.4 (827.9)	1834.6 (744.9)	2089.6 (630.7)
Tendon elongation (mm)	18.4 (3.2)	18.7 (2.2)	18.2 (4.5)	15.3 (3.0)
Stiffness (N/mm^2)	139.8 (49.9)	129.5 (51.0)	*109.4 (37.2)*^{C}	184.3 (65.6)
Young's modulus (GPa)	*0.33 (0.09)*^{C}	**0.30 (0.09)**^{C}	*0.30 (0.12)*^{C}	0.48 (0.22)
Tendon strain (%)	8.6 (1.6)	7.8 (1.2)	8.6 (2.2)	7.5 (1.1)
Tendon stress (MPa)	24.1 (5.8)	19.6 (5.7)	23.2 (10.5)	24.7 (8.3)
Energy utilisation				
Energy stored (kJ)	20.4 (5.6)	16.8 (9.7)	16.4 (11.4)	13.0 (5.7)
Energy released (kJ)	16.2 (4.3)	14.5 (7.4)	12.7 (7.6)	11.3 (5.0)
Mechanical hysteresis (%)	**20.1 (5.7)**^{C,H}	12.4 (4.0)	17.2 (9.7)	13.2 (4.7)

Values in bold font indicate those reaching significance ($P \leq .05$), and values in italics indicate those demonstrating trends towards significance ($P \leq .10$). L: vs low ABPI group (High disease severity); H: vs high ABPI group (low disease severity); A: vs asymptomatic-limb group; C: vs control group

Table 6. Backward step-wise regression between architectural parameters, tendon properties, and disease severity (ABPI) and walking endurance (ICD). Prediction equations are depicted for the model that explains the highest portion of variance (highest adjusted R^2) and the most efficient model (fewest parameters).

ICD	R	R^2	Adjusted R^2	*P*-value
Model 1	0.918	0.843	0.371	0.345
Model 2	0.918	0.843	0.528	0.179
Model 3	0.918	0.842	0.621	0.080
Model 4	0.908	0.825	0.649	0.041
Model 5	0.891	0.795	0.648	0.023
Model 6	0.842	0.710	0.565	0.027
Model 7	0.820	0.672	0.563	0.015

Prediction for Model 4 = 483.5 - (4.489*Hysteresis) + (0.027*Tendon Force) - (0.269*Tendon stiffness) + (4.044*GL pennation) - (11.401*GM pennation) - (136.36*ABPI)

Prediction for Model 7 = 506.690 – (4.935*Hysteresis) – (9.054*GM pennation) – (126.544*ABPI)

Model 1: ABPI, GM pennation, hysteresis, tendon stiffness, tendon force, GL pennation, GM fascicle : tendon length, GL fascicle : tendon length, strain
Model 2: ABPI, GM pennation, hysteresis, tendon stiffness, tendon force, GL pennation, GM fascicle : tendon length, GL fascicle : tendon length
Model 3: ABPI, GM pennation, hysteresis, tendon stiffness, tendon force, GL pennation, GM fascicle : tendon length
Model 4: ABPI, GM pennation, hysteresis, tendon stiffness, tendon force, GL pennation
Model 5: ABPI, GM pennation, hysteresis, tendon stiffness, tendon force
Model 6: ABPI, GM pennation, hysteresis, tendon stiffness
Model 7: ABPI, GM pennation, hysteresis

Table 7. Backward step-wise regression between architectural parameters, tendon properties, and disease severity (ABPI) and walking endurance (ACD). Prediction equations are depicted for the model that explains the highest portion of variance (highest adjusted R^2) and the most efficient model (fewest parameters).

ACD	R	R^2	Adjusted R^2	*P*-value
Model 1	0.892	0.796	0.184	0.460
Model 2	0.892	0.796	0.387	0.271
Model 3	0.890	0.793	0.499	0.145
Model 4	0.887	0.787	0.574	0.069
Model 5	0.873	0.762	0.593	0.037
Model 6	0.839	0.704	0.556	0.029
Model 7	0.798	0.637	0.516	0.023
Model 8	0.765	0.585	0.502	0.012
Model 9	0.699	0.489	0.442	0.008

Prediction for Model 5 = 1322.244 - (15.515*Hysteresis) + (0.099*Tendon Force) - (14.474*GL pennation) - (22.324*GM pennation) - (294.257*ABPI)

Prediction for Model 9 = 934.509 – (-23.988*GM pennation)

Model 1: GM pennation, tendon force, hysteresis, ABPI, GL pennation, tendon stiffness, strain, GM fascicle : tendon length, GL fascicle : tendon length
Model 2: GM pennation, tendon force, hysteresis, ABPI, GL pennation, tendon stiffness, strain, GM fascicle : tendon length
Model 3: GM pennation, tendon force, hysteresis, ABPI, GL pennation, tendon stiffness, strain
Model 4: GM pennation, tendon force, hysteresis, ABPI, GL pennation, tendon stiffness
Model 5: GM pennation, tendon force, hysteresis, ABPI, GL pennation
Model 6: GM pennation, tendon force, hysteresis, ABPI
Model 7: GM pennation, tendon force, hysteresis
Model 8: GM pennation, tendon force
Model 9: GM pennation

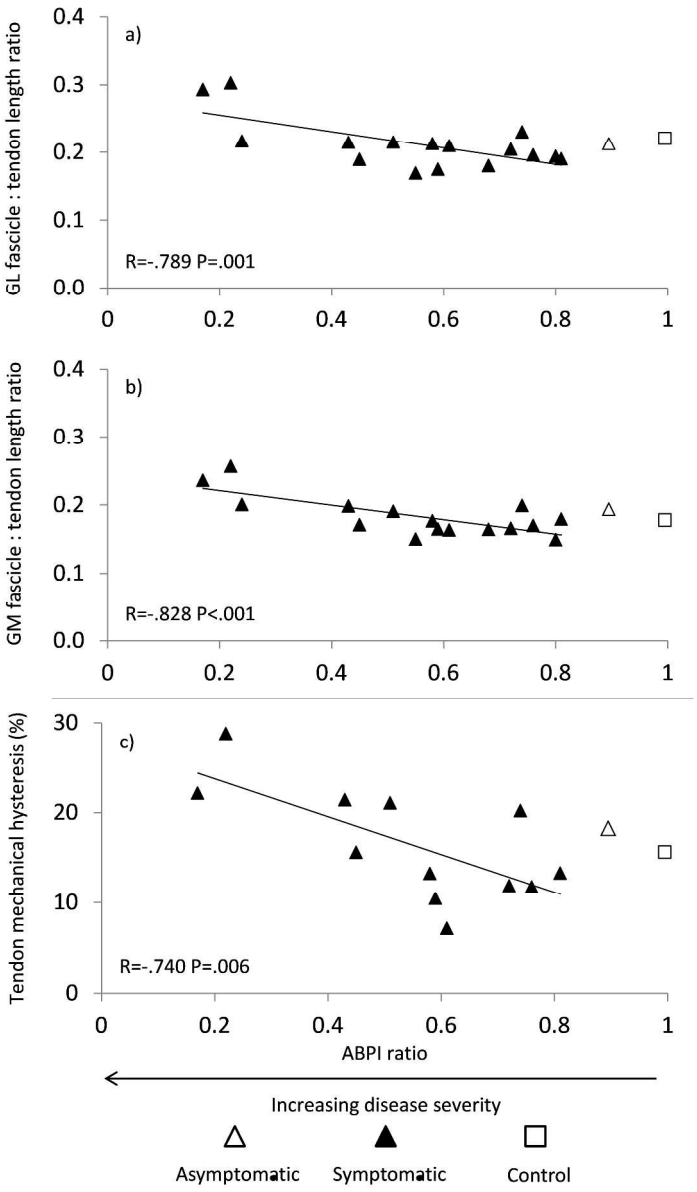

Figure 1. Correlations between disease severity (ABPI) and GL and GM fascicle : tendon length ratio (a and b respectively) and tendon mechanical hysteresis (c). Control and asymptomatic-limb groups are shown for comparison and are not included in correlation analysis
447x765mm (300 x 300 DPI)