Sex differences in the associations between L-arginine pathway metabolites, skeletal muscle mass and function, and their responses to resistance exercise, in old age

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Abstract

Objectives

The current study was designed to explore the associations between L-arginine metabolites and muscle mass and function in old age, which are largely unknown.

Design

The study used a randomised, double-blind, placebo-controlled design.

Setting

The study was carried out in a laboratory setting.

Participants

50 healthy older adults [median age 70 years (IQR 67-73); 27 males].

Intervention

Participants undertook an 18-week resistance exercise program, and a nutritional intervention (fish oil vs. placebo).

Measurements

Serum homoarginine, ornithine, citrulline, asymmetric dimethylarginine (ADMA), NG-monomethyl-L-arginine (L-NMMA), and symmetric dimethylarginine (SDMA), maximal voluntary contraction (MVC) and isokinetic torque of the knee extensors at 30° s^{-1} (MIT), muscle cross sectional area (MCSA) and quality (MQ) were measured at baseline and after the intervention.

Results

No significant exercise-induced changes were observed in metabolite concentrations. There were significant sex differences in the associations between metabolites and muscle parameters. After adjusting for age, glomerular filtration rate and fish oil intervention, citrulline (P=0.002) and ornithine (P=0.022) were negatively associated with MCSA at baseline in males but not females. However, baseline citrulline was negatively correlated with

exercise-induced changes in MVC (P=0.043) and MQ (P=0.026) amongst females. Furthermore, amongst males, baseline homoarginine was positively associated with exercise-induced changes in MVC (P=0.026), ADMA was negatively associated with changes in MIT (P=0.026), L-NMMA (p=0.048) and ornithine (P<0.001) were both positively associated with changes in MCSA, and ornithine was negatively associated with changes in MQ (P=0.039).

Conclusion

Therefore, barring citrulline, there are significant sex differences in the associations between L-arginine metabolites and muscle mass and function in healthy older adults. These metabolites might enhance sarcopenia risk stratification, and the success of exercise programs, in old age.

Key words: L-arginine metabolites, muscle mass, muscle function, old age, exercise.

Introduction

Advancing age is associated with a loss of muscle mass (sarcopenia) of 0.5-2% per year in humans [1]. The main problem associated with sarcopenia is the concomitant loss of muscle function, also known as dynapaenia. The latter increases the likelihood of falls and reduces quality of life in old age [2]. Sarcopenia had an estimated economic cost of $18.5 billion in the year 2000 in the USA [3]. Several factors have been suggested to contribute to the development of sarcopenia such as physical inactivity, alterations in protein metabolism, alterations to diet, chronic low grade inflammation and motor unit loss [4]. However, the precise aetiology remains to be established.

Nitric oxide (NO), an endogenous regulator of vascular homeostasis, synthesized by NO synthases (NOS) using the amino acid L-arginine as a substrate, is also involved in maintaining skeletal muscle homeostasis. There is good evidence that NO mediates force production, muscle blood flow regulation, myocyte differentiation, respiration, and glucose homeostasis [5]. However, measuring NO concentrations *in vivo* is problematic, given its relatively short half-life [6]. Investigating more stable, direct or indirect, biomarkers of NO synthesis in modulating muscle homeostasis might allow one to identify patients at risk of developing sarcopenia and/or benefitting from specific interventions, e.g. physical exercise. Homoarginine and the methylated arginines, asymmetric dimethylarginine (ADMA) and NG-monomethyl-L-arginine (L-NMMA), have been shown to modulate, either positively (homoarginine) or negatively (ADMA and L-NMMA), NO synthesis [7-9]. The potential role of these metabolites in skeletal muscle homeostasis is supported by recent studies reporting cross-sectional association trends between homoarginine, ADMA and muscle strength in older populations [10, 11]. However, we are currently lacking data on the association between L-arginine pathway metabolites and comprehensive measures of muscle function, as well as muscle mass. Furthermore, as resistance exercise improves muscle function in older adults

[12], it would be of interest to determine whether specific L-arginine metabolites prior to resistance exercise are associated with the changes in muscle mass and function following exercise.

The main aim of this study was to investigate the cross-sectional associations between L-arginine pathway metabolites, muscle mass and function, in a cohort of healthy older adults. A secondary aim was to determine associations between pre-exercise L-arginine metabolites and changes in muscle mass and function after resistance exercise training. A group of healthy older adults without a history of chronic disease was selected to minimize the confounding impact of medications and disease states on skeletal muscle homeostasis [13, 14].

Methods

Study population

Fifty community-dwelling adults >65 years old (27 males and 23 females) were recruited. Participants had no history of cardiovascular disease, cancer, arthritis, respiratory disease, metabolic disease, recent fractures and loss of mobility. No subject was on daily analgesia, nutritional supplements, or participating in any resistance exercise training. However, two participants were taking medications: one female participant was prescribed angiotensin converting enzyme inhibitors for mild hypertension, and one male participant was prescribed allopurinol for gout. The study was approved by the University of Aberdeen College of Life Sciences and Medicine Ethics Review Board (CERB/2011/6/644) and registered at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02843009). Written consent was obtained after explanation of the aims, risks and potential discomfort associated with the study, which conformed to the declaration of Helsinki. These participants were part of a study investigating

the effects of fish oil consumption on adaptations to resistance exercise and so were randomly assigned to either consume 3.0 g/day safflower oil or 3.0 g/day fish oil [15].

Resistance exercise training

Resistance exercise training was performed twice weekly for 18 weeks. Each training session included four sets of nine repetitions for each exercise: leg press, leg extension, leg curl and calf press. The load for each exercise was set at 70% of the participant's one repetition maximum (1RM). This was assessed for each exercise at baseline and every six weeks, and the load re-adjusted accordingly.

Muscle mass and function

The following measurements were performed the morning after an overnight fast, as previously described [16]. Measurements were made prior to and at least 48-h after the completion of the resistance exercise training intervention.

Knee extensor isometric and isokinetic torque

Maximal isometric torque of the knee extensor muscles of the right leg was determined during a maximal voluntary contraction (MVC) with the participant seated on a Biodex dynamometer with a knee angle of 73°. With the same seating position, maximal isokinetic torque (MIT) of the knee extensors was measured at 30° s^{-1}.

Magnetic resonance imaging (MRI)

Of the 50 subjects completing the intervention 45 were able to participate in MRI data collection (3 were claustrophobic and 2 had metal implants). All scans were carried out on a Philips Achieva 3.0 Tesla whole body MRI scanner using a 16-channel SENSE XL Torso

coil. Muscle Anatomical Cross Sectional Area (MCSA) was quantified mid-thigh. Muscle quality (MQ) was calculated as torque (knee extensor isometric strength) per unit MCSA.

Anthropometric parameters

Body weight, height and body mass index (BMI) were measured in each study participant at baseline.

Biochemical parameters

Before and after the intervention fasted blood samples were collected from a vein in the antecubital fossa into K^+EDTA vacutainers, placed on ice and processed within 30 min. Samples were centrifuged for 10 min at 4 °C at 800*g* and plasma aliquoted and stored at -80 °C until analysis.

L-arginine metabolites, creatinine, creatine, and glomerular filtration rate

An Aquity UPLC (Waters, Sydney, Australia) coupled to a qToF Premier high-resolution mass spectrometer (Waters, Sydney, Australia) was used to measure plasma concentrations of L-arginine, ADMA, citrulline, homoarginine, L-NMMA, ornithine, SDMA, creatinine and creatine (for details see Supplementary file). The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease formula [17].

Statistical analysis

Results are expressed as means ± SD, medians and interquartile ranges, or frequencies as appropriate. Variables were tested for normal distribution by using the Kolmogorov-Smirnov test. Between-group differences were assessed either by one-way ANOVA (normally distributed variables) or Mann-Whitney U test (non-normally distributed variables). Differences between baseline and post-exercise muscle mass and function were assessed

either by paired Student's t-test (normally distributed variables) or Wilcoxon test (non-normally distributed variables). In each sex, the effects of exercise and nutritional intervention on L-arginine metabolites, creatinine and creatine, were assessed by ANCOVA. Partial correlations, stratified by sex and adjusted for age and eGFR, assessed the relationship between L-arginine metabolites and parameters of skeletal muscle mass and function (MVC: primary outcome; MIT, MCSA and MQ: secondary outcomes). Analyses were adjusted for age, eGFR and fish oil supplementation as these factors influence both L-arginine metabolite concentrations and muscle strength and volume [15, 18-20]. Analyses were performed using IBM SPSS Statistics Version 23, Release 23.0.0.2 (SPSS Inc., Armonk, NY, USA). A two-sided $P<0.05$ indicated statistical significance.

Results

Baseline characteristics

There were no significant sex-related differences in age, BMI, eGFR and MQ (Table 1). MVC, MIT, MCSA and serum creatinine concentrations were significantly higher in males, whereas serum creatine concentrations were significantly higher in females. Serum L-arginine, ADMA, L-NMMA, SDMA, ornithine and citrulline concentrations were similar in both sexes. However, serum homoarginine concentrations were significantly higher in males.

Effects of exercise training on muscle parameters and arginine metabolites

The 18-week resistance exercise training induced a significant increase in MVC (31 ± 24 %, $P<0.001$), MIT (12 ± 18 %, $P<0.001$), MCSA (3 ± 5 %, $P<0.001$) and MQ (27 ± 26 %, $P<0.001$) in the whole group, with similar effects in both sexes. Barring a significant reduction in serum L-arginine concentrations in males, there were no significant baseline vs. post-exercise differences in L-arginine metabolites, creatinine and creatine in both sexes (Table 2).

Females

Baseline

There were no significant correlations between L-arginine metabolites and parameters of muscle structure and function at baseline (Table 3).

Exercise-induced changes

There were significant negative correlations between baseline citrulline concentrations and exercise-induced changes in MVC and MQ, and a negative trend between citrulline and exercise-induced changes in MIT (Table 4). By contrast, no significant correlations were observed between homoarginine, ADMA, L-NMMA, SDMA, and ornithine and exercise-induced changes in muscle structure and function.

Males

Baseline

There were significant negative correlations between baseline ornithine and citrulline concentrations and MCSA. By contrast, there were no significant correlations between homoarginine, ADMA, L-NMMA, and SDMA and muscle parameters (Table 5).

Exercise-induced changes

Significant positive correlations were observed between homoarginine concentrations and MVC changes, and L-NMMA and ornithine concentrations and MCSA changes (Table 6). A positive trend was also observed between homoarginine and MQ changes. By contrast, significant negative correlations were observed between ADMA concentrations and MIT changes, and between ornithine concentrations and MQ changes.

Discussion

We observed significant sex differences in the associations between specific L-arginine pathway metabolites and established parameters of muscle structure and function in a cohort of healthy older adults undertaking an exercise program. Negative correlations, either at baseline or after exercise-induced changes, were observed in both sexes between citrulline and muscle parameters. However, further correlations with ornithine, homoarginine, ADMA and L-NMMA, direct or indirect modulators of NO synthesis, were observed in males, but not females. The observed correlations were adjusted for age, eGFR and nutritional intervention.

The negative correlations between serum citrulline concentrations and parameters of muscle structure and function in both older females and males is intriguing. Citrulline is a by-product of both the enzymatic synthesis of NO by NOS and of the catabolism of L-NMMA and ADMA by dimethylarginine dimethylaminohydrolase (DDAH) [21]. Ornithine, a product of the bioconversion of arginine by the enzyme arginase [22], also showed a significant negative correlation with baseline MCSA, but a significant positive association with exercise-induced MCSA changes, in males. There is good evidence that an increase in arginase activity, therefore an increased synthesis of ornithine and, potentially, citrulline, is associated with endothelial dysfunction and alterations in vascular homeostasis, possibly through reduced supply of L-arginine needed by NOS to produce NO or through direct vasculotoxic effects of ornithine [23]. This, in turn, might lead to reduced skeletal muscle blood flow and other alterations previously described as a result of reduced NO synthesis, particularly in males [5]. Elevations in ornithine concentrations might not only represent a marker of reduced MCSA at baseline, but could also identify subjects exhibiting a greater MCSA response after exercise. However, in view of the negative correlations observed between ornithine and exercise-induced changes in MQ, further studies are needed to establish the role of ornithine and citrulline in sarcopenia risk stratification and response to exercise in old age.

Serum concentrations of homoarginine, a non-essential and non-proteinogenic amino acid synthesized from L-arginine by the enzyme arginine:glycine aminidino transferase (AGAT), were positively correlated with exercise-induced changes in MVC in males. It has been proposed that homoarginine is a substrate for NOS. The possible beneficial effects of higher homoarginine might be secondary to an increased NO synthesis either in myocytes or in the local arterial circulation. The latter has been shown to positively affect force production, muscle blood flow regulation, myocyte differentiation, respiration, and glucose homeostasis [5]. Moreover, endothelial dysfunction, a consequence of impaired NO synthesis, has been shown to reduce the anabolic effects of insulin on amino acid delivery, thus favoring the onset of sarcopenia [24]. Another potential beneficial effect of homoarginine on skeletal muscle involves its biosynthesis by AGAT, significantly expressed in myocytes [25], which also results in the formation of guanidinoacetate. The latter is further converted into creatine, by guanidinoacetate methyltransferase [26], which is known to be beneficial for muscle mass and function in older adults [27].

We observed significant sex differences in serum homoarginine concentrations, with higher concentrations in males, in accordance with previous reports [28]. Putative mechanisms explaining the higher concentrations of homoarginine in males include a) the positive effects of methyltestosterone on guanidinoacetate, and possibly homoarginine, synthesis [29]; and b) the estrogen-mediated up-regulation of the cationic amino acid transporter 1, which facilitates the transport of homoarginine and other analogues into the cytoplasm, thus reducing circulating concentrations [30]. However, the latter hypothesis is not supported by the lack of significant sex-related differences in other arginine analogues interacting with this transporter, e.g. ADMA, SDMA and L-NMMA, in our study. In a previous study in older female nursing home patients, Pilz et al observed an association trend between serum homoarginine concentrations and higher knee extensor strength (P=0.065) after adjusting for age, BMI,

albumin, creatinine clearance and parathyroid hormone concentrations [10]. Our study provides additional evidence of a potential beneficial homoarginine-mediated effect on muscle homeostasis, particularly in males.

The potential role of NO in modulating muscle structure and function in old age, particularly in males, is further supported by the negative correlation observed between ADMA, an endogenous NOS inhibitor, and exercise-induces changes in MIT in this group. ADMA-mediated inhibition of NO synthesis might lead to endothelial dysfunction, reduced muscle blood flow and alterations in muscle metabolism, as previously described [5, 24]. However, the observation of a positive association between L-NMMA, another endogenous NOS inhibitor, and MCSA, challenges this theory. Nevertheless, Obayashi et al have recently reported significant negative associations between serum ADMA concentrations, reduced grip strength (P=0.001) and quadriceps strength (P=0.012 in a larger cohort of community-dwelling older Japanese male and female adults [11].

The observation of sex-specific correlations between L-arginine pathway metabolites and skeletal muscle mass and function is potentially relevant for several reasons. First, it suggests that the relationship between L-arginine metabolic pathways and muscle homeostasis is different between older males and females. Second, it might lead to the identification of novel biomarkers of either impaired muscle homeostasis and/or risk of sarcopenia in old age. Third, it might predict the outcome of exercise programs in specific patient groups. Fourth, it might help in the design of nutritional interventions targeting NO synthesis.

Strengths of our study included the rigorous assessment of a comprehensive panel of L-arginine metabolites and established parameters of muscle mass and function, the limited confounding effect of age-associated co-morbid states and prescribed medications, and the closely supervised exercise training program in all participants. Furthermore, the longitudinal

nature of the study design allowed predicting changes in the outcomes of interest, thereby increasing the evidence for causality. Limitations include the relatively small sample size and the generalizability of our findings to other older patient populations, particularly frail patients with significant sarcopenia and co-morbidity burden.

In conclusion, our study suggests that specific L-arginine metabolites, directly or indirectly influencing NO synthesis, might play an important role in the modulation of skeletal muscle mass and function in old age, particularly in males. Pending further confirmation in different populations, the identified biomarkers of NO synthesis and muscle homeostasis might enhance sarcopenia risk stratification, and the success of exercise programs, in this patient group.

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Ethics declaration

All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the University of Aberdeen College of Life Sciences and Medicine Ethics Review Board (CERB/2011/6/644).

Conflicts of interest

The authors do not have any conflicts of interest to declare.

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Table 1. Baseline characteristics

Parameter	**Whole group (n=50)**	**Males (n=27)**	**Females (n=23)**	**P-value***
Age (years)	70 [67, 73]	69 [67, 72]	71 [68, 73]	0.544
Height (cm)	169 [159, 176]	175 [172, 179]	159 [155, 168]	<0.0001
Weight (Kg)	72.1±15.1	78.1±15.0	65.1±12.3	0.002
Body Mass Index (Kg/m^2)	25.4±4.4	25.6±4.2	25.3±4.7	0.821
Estimated GFR (mL/min)	80±12	77±12	83±13	0.079
Creatine (μmol/L)	168±76	134±51	208±83	0.001
Creatinine (μmol/L)	79±12	85±10	71±9	<0.0001
Maximal voluntary contraction (N•m)	90 [75, 120]	115 [94, 138]	76 [68, 85]	<0.0001
Maximal isokinetic torque (N•m)	116±37	141±32	86±14	<0.0001
Muscle ACSA (cm^2)	51 [38, 64]	63 [58, 68]	37 [32, 43]	<0.0001
Muscle quality ($N•m/cm^2$)	2.0±0.5	1.9±0.5	2.1±0.5	0.293
Arginine (μmol/L)	305±44	302±50	309±36	0.580
Homoarginine (μmol/L)	2.36±0.76	2.74±0.67	1.90±0.60	<0.0001
Asymmetric dimetylarginine (μmol/L)	0.52±0.10	0.52±0.11	0.52±0.10	0.999
NG-monomethyl-L-arginine (μmol/L)	0.05 [0.04, 0.06]	0.05 [0.03, 0.05]	0.05 [0.04, 0.07]	0.108
Symmetric dimethylarginine (μmol/L)	0.48±0.12	0.48±0.08	0.48±0.15	0.950
Ornithine (μmol/L)	84 [80, 94]	87 [81, 101]	83 [72, 89]	0.060
Citrulline (μmol/L)	40 [35, 49]	39 [33, 48]	41 [37, 49]	0.360

Data shown as mean ± SD or median [IQR] as appropriate

Legend: GFR, glomerular filtration rate; ACSA, anatomical cross sectional area; *, males vs. females.

Table 2. Baseline vs. post-exercise mean (95% CI) differences in arginine metabolites, creatinine, and creatine in males and females

	Mean (95% CI) difference	**P-value**
Females		
Arginine	-8 (-29 to 12)	0.393 #
Homoarginine	+0.13 (-0.06 to 0.32)	0.184
Asymmetric dimethylarginine	-0.01 (-0.06 to 0.05)	0.839
NG-monomethyl-L-arginine	-0.01 (-0.02 to 0.00)	0.153
Symmetric dimethylarginine	-0.05 (-0.11 to 0.01)	0.097
Ornithine	-0.48 (-6.45 to 5.49)	0.869 #
Citrulline	-0.42 (-3.67 to 2.83)	0.790
Creatinine	-2 (-5 to 2)	0.322
Creatine	+2 (-23 to 26)	0.883
Males		
Arginine	-27 (-47 to -7)	0.010
Homoarginine	-0.06 (-0.41 to 0.30)	0.745
Asymmetric dimethylarginine	+0.01 (-0.05 to 0.06)	0.883
NG-monomethyl-L-arginine	0.00 (-0.01 to 0.01)	0.566 #
Symmetric dimethylarginine	-0.02 (-0.05 to 0.01)	0.204
Ornithine	-6.5 (-13.8 to -.74)	0.076
Citrulline	-0.84 (-2.84 to 1.17)	0.398
Creatinine	-2 (-5 to 1)	0.265
Creatine	-6 (-20 to 9)	0.428

#, time * nutritional intervention interaction ($P<0.05$).

Table 3. Partial correlations* between baseline arginine metabolites and parameters of muscle mass and function in females

	MVC (N•m)	**MIT (N•m)**	**MCSA (cm^2)**	**MQ ($N•m.cm^2$)**
Arginine	r= -0.38 P=0.129	r= -0.39 P=0.118	r= +0.02 P=0.946	r= -0.34 P=0.181
HMA	r= -0.26 P=0.314	r= +0.06 P=0.814	r= -0.36 P=0.160	r= +0.05 P=0.834
ADMA	r= +0.04 P=0.880	r= +0.40 P=0.110	r= +0.42 P=0.092	r= -0.31 P=0.222
L-NMMA	r= -0.03 P=0.907	r= +0.28 P=0.281	r= +0.34 P=0.179	r= -0.24 P=0.357
SDMA	r= +0.06 P=0.813	r= +0.18 P=0.478	r= +0.08 P=0.750	r= -0.02 P=0.949
Ornithine	r= -0.28 P=0.281	r= -0.23 P=0.371	r= -0.25 P=0.329	r= -0.03 P=0.907
Citrulline	r= +0.25 P=0.329	r= +0.19 P=0.475	r= -0.15 P=0.573	r= +0.31 P=0.233

*, adjusted for age and estimated glomerular filtration rate

Legend: MVC, maximal voluntary contraction; MIT, maximal isokinetic torque; MCSA, muscle volume; MQ, muscle quality; HMA, homoarginine; ADMA, asymmetric dimethylarginine; L-NMMA, NG-monomethyl-L-arginine; SDMA, symmetric dimethylarginine.

Table 4. Partial correlations* between baseline arginine metabolites and post-exercise changes in parameters of muscle mass and function in females

	Δ%MVC (N•m)	**Δ%MIT (N•m)**	**Δ%MCSA (cm^2)**	**Δ%MQ (N•m.cm^2)**
Arginine	r= +0.03 P=0.922	r= -0.24 P=0.364	r= -0.37 P=0.157	r= -0.26 P=0.337
HMA	r= +0.18 P=0.501	r= -0.01 P=0.988	r= +0.07 P=0.789	r= -0.05 P=0.852
ADMA	r= +0.10 P=0.713	r= -0.42 P=0.108	r= +0.04 P=0.892	r= +0.18 P=0.505
L-NMMA	r= +0.14 P=0.604	r= -0.34 P=0.191	r= +0.08 P=0.780	r= -0.29 P=0.283
SDMA	r= -0.10 P=0.713	r= -0.18 P=0.504	r= +0.24 P=0.374	r= -0.21 P=0.444
Ornithine	r= +0.33 P=0.213	r= +0.03 P=0.914	r= -0.33 P=0.212	r= +0.25 P=0.358
Citrulline	**r= -0.51** **P=0.043**	r= -0.48 P=0.060	r= +0.04 P=0.890	**r= -0.55** **P=0.026**

*, adjusted for age, estimated glomerular filtration rate, and intervention group

Legend: MVC, maximal voluntary contraction; MIT, maximal isokinetic torque; MCSA, muscle volume; MQ, muscle quality; HMA, homoarginine; ADMA, asymmetric dimethylarginine; L-NMMA, NG-monomethyl-L-arginine; SDMA, symmetric dimethylarginine.

Significant correlations (P<0.05) are highlighted in bold.

Table 5. Partial correlations* between baseline arginine metabolites and parameters of muscle mass and function in males

	MVC (N•m)	**MIT (N•m)**	**MCSA (cm^2)**	**MQ ($N•m.cm^2$)**
Arginine	r= -0.14 P=0.538	r= +0.02 P=0.912	**r= -0.45** **P=0.035**	r= +0.07 P=0.743
HMA	r= +0.11 P=0.619	r= +0.27 P=0.221	r= +0.24 P=0.289	r= -0.04 P=0.851
ADMA	r= -0.06 P=0.802	r= +0.22 P=0.320	r= -0.01 P=0.989	r= -0.08 P=0.730
L-NMMA	r= -0.33 P=0.139	r= -0.28 P=0.201	r= -0.36 P=0.100	r= -0.14 P=0.522
SDMA	r= -0.13 P=0.552	r= -0.12 P=0.590	r= -0.16 P=0.477	r= -0.04 P=0.871
Ornithine	r= -0.05 P=0.808	r= -0.05 P=0.817	**r= -0.48** **P=0.022**	r= +0.22 P=0.321
Citrulline	r= -0.32 P=0.144	r= -0.33 P=0.132	**r= -0.63** **P=0.002**	r= -0.01 P=0.990

*, adjusted for age and estimated glomerular filtration rate

Legend: MVC, maximal voluntary contraction; MIT, maximal isokinetic torque; MCSA, muscle volume; MQ, muscle quality; HMA, homoarginine; ADMA, asymmetric dimethylarginine; L-NMMA, NG-monomethyl-L-arginine; SDMA, symmetric dimethylarginine.

Significant correlations (P<0.05) are highlighted in bold.

Table 6. Partial correlations* between baseline arginine metabolites and post-exercise changes in parameters of muscle mass and function in males

	Δ%MVC (N•m)	**Δ%MIT (N•m)**	**Δ%MCSA (cm^2)**	**Δ%MQ ($N•m.cm^2$)**
Arginine	r= -0.12 P=0.598	r= -0.42 P=0.059	r= +0.21 P=0.356	r= -0.17 P=0.463
HMA	**r= +0.48** **P=0.026**	r= +0.30 P=0.189	r= +0.23 P=0.309	r= +0.40 P=0.068
ADMA	r= -0.29 P=0.198	**r= -0.49** **P=0.023**	r= +0.37 P=0.101	r= -0.37 P=0.096
L-NMMA	r= +0.14 P=0.557	r= -0.06 P=0.793	**r= +0.44** **P=0.048**	r= +0.03 P=0.909
SDMA	r= +0.17 P=0.449	r= +0.06 P=0.781	r= +0.04 P=0.846	r= +0.16 P=0.476
Ornithine	r= -0.30 P=0.191	r= -0.25 P=0.271	**r= +0.723** **P<0.001**	**r= -0.45** **P=0.039**
Citrulline	r= -0.24 P=0.293	r= -0.32 P=0.163	r= +0.25 P=0.265	r= -0.29 P=0.209

*, adjusted for age, estimated glomerular filtration rate, and intervention group

Legend: MVC, maximal voluntary contraction; MIT, maximal isokinetic torque; MCSA, muscle volume; MQ, muscle quality; HMA, homoarginine; ADMA, asymmetric dimethylarginine; L-NMMA, NG-monomethyl-L-arginine; SDMA, symmetric dimethylarginine.

Significant correlations (P<0.05) are highlighted in bold.