



Structural severity, phase angle, and quadriceps strength among patients with knee osteoarthritis: the SPSS-OK study

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Abstract

Introduction/objectives The associations between severity of knee osteoarthritis (KOA) and phase angle (PhA) and between PhA and quadriceps strength in patients with KOA are unclear. This study examined (1) whether the structural severity of KOA affects PhA and (2) whether PhA affects quadriceps strength in patients with KOA.

Method Data of 1093 patients with KOA, obtained from Screening for People Suffering Sarcopenia in the Orthopedic cohort of Kobe study, were analyzed. PhA was determined by bioimpedance. Quadriceps strength was measured using a handheld dynamometer. Structural severity of KOA was determined using Kellgren-Lawrence radiographic grading scale. A series of general linear models were fitted to estimate the magnitude of differences in PhA by differences in KOA severity and quadriceps strength by differences in PhA.

Results The mean age of the patients was 72.8 years, and 78% were women. Increasing KOA severity was associated with decreasing PhA, especially in men. In women, only grade 4 KOA was associated with a decrease in PhA (P for interaction = 0.048). PhA per leg was positively associated with quadriceps strength per leg, independent of age, sex, leg muscle mass, pain, and KOA severity (mean difference per 1° increase = 7.54 Nm, 95% confidence interval = 5.51–9.57 Nm). The association between PhA and quadriceps strength differed neither by sex nor by KOA severity (P for interaction = 0.133 and 0.185, respectively).

Conclusions PhA decreased with increasing KOA severity, and increasing PhA was associated with increasing quadriceps strength. Clinicians should, therefore, evaluate PhA to assess quadriceps strength in patients with KOA.

Key Points

- PhA gradually decreased with increasing severity of KOA, especially in men.
- Increasing PhA was associated with increasing quadriceps strength.
- Clinicians should focus on increasing muscle mass and PhA.

Keywords Knee osteoarthritis · Phase angle · Quadriceps strength · Structural severity

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Introduction

Quadriceps strength is a modifiable factor that determines functional movement regardless of the severity of knee osteoarthritis (KOA), as assessed by radiography [1]. It is associated with leg muscle mass in patients with KOA [2]. Recently, for the exertion of strength, attention has been paid not only to the volume of leg muscles but also to other indices related to muscle quality. As such, phase angle (PhA) has been investigated.

PhA can be calculated simultaneously with muscle mass via bioelectrical impedance using the following two measures: reactance (cell membrane-specific resistance, X_c) and resistance (intracellular and extracellular resistance, R). Theoretically, X_c is an index of the volume of cell membrane capacitance, and resistance to electrical current is determined by body fat, total body water, and extracellular water [3]. Therefore, PhA reflects electric tissue property and is considered a marker of cell membrane integrity [4]. Some researchers pointed out that disease or impairment in functional movement can disturb electrical properties of tissue and directly lower PhA [5]. Considering this possibility of disease-dependent change in PhA [5], severe KOA may theoretically reduce PhA. In support of this hypothesis, a previous study showed that PhA in patients with severe KOA was lower than that in patients with early KOA [6]. However, the study did not investigate the relationship between the grade of KOA and PhA, taking into consideration of other demographics such as age and sex. In addition, PhA has been associated with muscle strength among the general elderly population [7], but the association between PhA and quadriceps strength in patients with KOA remains unclear.

In this study, using data from the “Screening for People Suffering Sarcopenia in Orthopedic cohort of Kobe” (SPSS-OK) study—a large, single-center study—we aimed to investigate (1) whether KOA severity is associated with reduced PhA and (2) whether PhA is associated with quadriceps strength in patients with KOA. We hypothesize that there is an association between increasing severity of KOA and a decrease in PhA, and one between an increase in PhA and increasing quadriceps strength.

Materials and methods

Design, setting, and participants

This was a cross-sectional study. Patients were recruited consecutively from August 2016 to January 2019. The study center is located in the central part of Kobe, Japan. Only patients with KOA who were scheduled for their first knee replacement surgery were included, to avoid the potential interference of implants on bioimpedance analysis (BIA). The exclusion criteria were stroke, Parkinson’s disease, severe cognitive

impairment, severe psychiatric impairment, and severe cardiac, pulmonary, or musculoskeletal disorders that limited walking and quadriceps strength. In addition, we excluded older adults with artificial implants such as cardiac pacemakers and joints, which did not permit the measurement of bioelectrical impedance. BIA data, quadriceps strength, radiographs of both knees, and other covariates were measured within 2 months before surgery. Based on the radiographs, a diagnosis of KOA was made by orthopedic surgeons, according to the American College of Rheumatology criteria [8]. The study was approved by the local institutional review board (no. 57, January 26, 2017) and the Research Ethics Committee of Fukushima Medical University School of Medicine (no. 2850, September 28, 2016). All patients provided written informed consent prior to participation. Because the study aimed to discover the association of KOA severity with PhA and that of PhA with quadriceps strength, sample size calculation was not pre-specified [9].

Conceptual framework

The conceptual framework is shown in Fig. 1. First, we evaluated the relationship between KOA severity as the exposure variable and PhA as the outcome variable, with sex as the effect modifier (analysis no. 1). Next, we assessed the relationship between PhA as the exposure variable and quadriceps strength as the outcome variable, with KOA severity as the effect modifier (analysis no. 2).

KOA severity

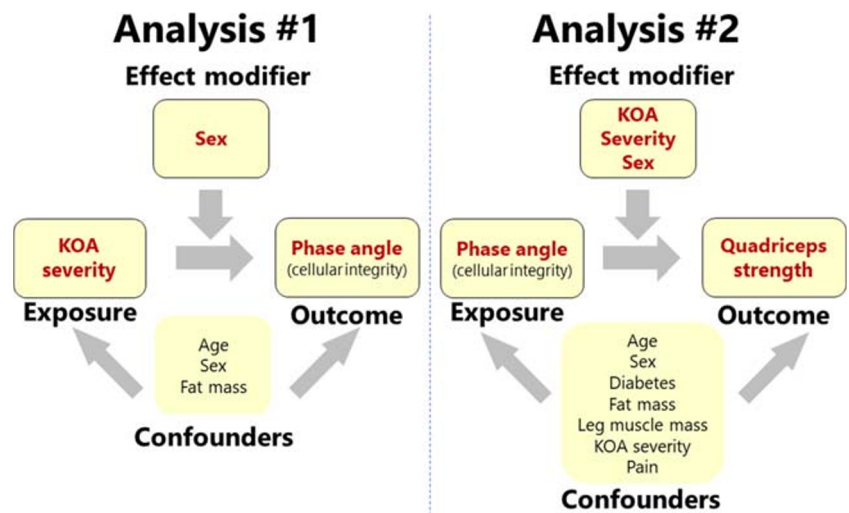
One trained observer (OW) graded KOA severity, using the patients’ radiographs, based on the Kellgren-Lawrence radiographic grading system [10]. Intra-rater reliability for radiographic severity was determined by the reassessment of 100 randomly selected radiographs 2 weeks later and was found to be excellent ($\kappa = 0.89$).

Bioelectrical impedance and PhA

A biometrical impedance system (MC-780A; TANITA CO, Ltd., Tokyo, Japan) was used to measure single-leg PhA and leg muscle mass. The monitor is a multifrequency device that measures bioimpedance at three frequencies between 5 and 250 kHz to directly measure the amount of extracellular and intracellular water in the body. The results were analyzed by an onboard body composition analyzer.

Single-leg PhA was calculated using the following formula: $\text{PhA (degrees)} = \arctangent(X_c/R) \times (180/\pi)$. Single-leg resistance and reactance, measured at 50 kHz, were used to calculate the single-leg PhA [3]. Thus, leg PhA was derived for both legs, regardless of the side planned for surgery.

Fig. 1 Conceptual framework used in the regression analyses. Outcome 1 was whether KOA severity would be associated with PhA and whether the associations differed by sex. Outcome 2 was whether PhA would be associated with quadriceps strength and whether the associations differed by KOA severity or by sex. KOA, knee osteoarthritis; PhA, phase angle



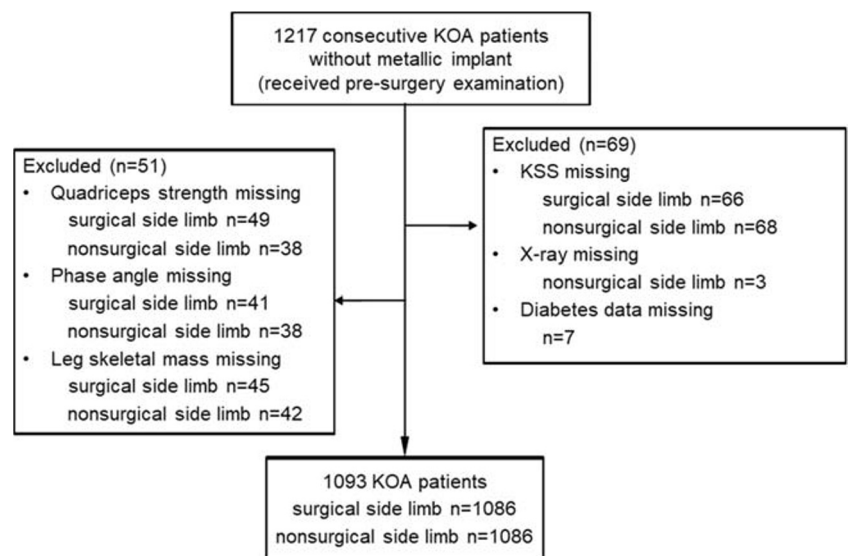
Quadriceps strength

Quadriceps strength was measured as the peak isometric knee extension torque (Nm) using a handheld dynamometer (µTas F1; Anima, Chofu, Japan). This method uses a belt to measure the strength of knee extension and is highly reliable [11]. Patients were seated with their hips flexed to 90°, and knees flexed to 75°. Following submaximal efforts, patients performed two maximal trials for 3 s while receiving verbal encouragement to facilitate maximal volitional force production. The distance between the attachment of the dynamometer and center of rotation of the knee joint was used as the lever arm length. The peak force (Newton) from two maximal contractions was multiplied by the lever arm length (m) and recorded as quadriceps strength.

Measurement of covariates

The examined covariates included sociodemographic characteristics, including age, fat mass measured by bioimpedance, type 2 diabetes, knee pain, and leg muscle mass. Type 2 diabetes was defined as glycosylated hemoglobin (HbA1c) level ≥ 6.5% [12], and the knee pain per leg was estimated using the 1-item new Knee Society Score (KSS) while walking on level ground; the score ranged from 0 = no pain to 10 = worst pain [13]. Muscle mass per leg was assessed as a proxy for quadriceps muscle mass. Quadriceps muscle mass accounts for approximately one quarter of the total single leg muscle volume, with the vastus lateralis, vastus medialis, vastus intermedius, and rectus femoris muscles contributing approximately 12%,

Fig. 2 Patient flow. Patients with missing exposure and outcome variables were excluded from the analyses. Finally, only 1093 patients were included. KOA, knee osteoarthritis; KSS, the new Knee Society Score



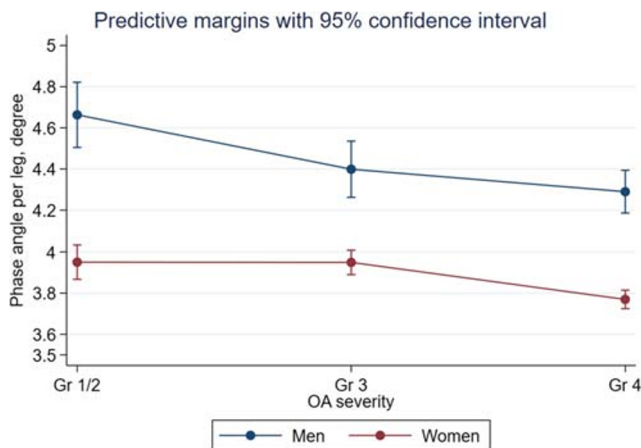


Fig. 3 Predicted phase angles by KOA severity per leg for each sex. Using the multivariable-adjusted general linear model including age, sex, fat mass, KOA severity, and interaction terms of sex and KOA severity, adjusted mean phase angles by KOA severity were predicted for each sex. Solid blue circles indicate point estimates for men. Solid red circles indicate point estimates for women. Error bars indicate 95% confidence intervals. KOA, knee osteoarthritis

6%, 4%, and 4%, respectively [14]. Validation of the BIA method using dual-energy x-ray absorptiometry (DXA) (DPX-L, GE Healthcare, Madison, WI, USA) showed very high correlations between the two methods for both fat mass and appendicular skeletal muscle mass [2].

Statistical analysis

All statistical analyses were conducted with Stata/SE version 15 (Stata Corp., College Station, TX). Complete case analyses were performed because a small proportion of patients had missing data. Characteristics were described using summary statistics: mean and standard deviation for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and number and proportion for categorical variables. The unit of analysis was limbs for both analyses no. 1 and no. 2 (i.e., PhA and quadriceps strength in analyses no. 1 and no. 2, respectively), as the outcome variable and some predictor variables (i.e., KOA severity in analysis no. 1 and PhA and leg muscle mass in no. 2) are limb-specific [15]. For this reason, we fitted general linear models with a cluster-robust variance to account for the correlation of paired outcome data among individuals [16]. For analysis no. 1, we estimated mean differences in PhA by differences in KOA severity (treated as categorical variable). The details of these analyses to examine sex-specific differences in the association between KOA severity and PhA are described in Supplementary Text 1. For analysis no. 2, we estimated mean differences in quadriceps strength by differences in PhA, with adjustment for age,

Table 1 Baseline characteristics of patients with KOA

	Total	
	N = 1093	
Age, years ^a	72.8	(8.0)
Female, n (%)	854	(78%)
Fat mass, kg ^a	20.4	(7.9)
Diabetes, n (%)	119	(11%)
X-ray grade, n (%)		
Surgical side		
Grade 1	0	(0%)
Grade 2	55	(5%)
Grade 3	223	(20%)
Grade 4	815	(75%)
Non-surgical side		
Grade 1	13	(1%)
Grade 2	270	(25%)
Grade 3	306	(28%)
Grade 4	501	(46%)
Missing n = 3		
Leg skeletal mass, kg ^a		
Surgical side	6.7	(1.7)
Non-surgical side	6.7	(1.7)
Phase angle, degree ^a		
Surgical side	3.8	(0.7)
Non-surgical side	4.1	(0.7)
Missing n = 1		
Quadriceps strength, Nm ^b		
Surgical side	48.3	[35.1; 64.2]
Missing n = 4		
Non-surgical side	58.5	[45.5; 75.9]
Missing n = 2		
KSS on walking on level ground, points ^b		
Surgical side	5	[3; 8]
Missing n = 3		
Non-surgical side	2	[0; 5]
Missing n = 2		

^a Continuous variables summarized as mean and standard deviation (in parentheses)

^b Continuous variables summarized as median and interquartile range (in square brackets)

The 1093 patients all had complete data on quadriceps strength, KSS, and knee x-rays for either the surgical side or non-surgical side. Notwithstanding the inclusion criteria, KSS may still have been missing in cases in which it was unavailable for one side but available for the other side. Complete data for either side (namely, 2172 limbs) were used for statistical analyses presented in Tables 2 and 3 and Figs. 3 and 4

KOA knee osteoarthritis, KSS the new Knee Society Score

sex, diabetes, fat mass, KSS, leg muscle mass, and KOA severity. The details of these analyses to examine KOA

Table 2 Associations between KOA severity and phase angle

Phase angle per leg, degree	Mean difference	(95% CI)		P value
Sex-adjusted model ^a				
X-ray severity for men				
1 or 2	Reference			
3	-0.32	(-0.53	to -0.10)	0.004
4	-0.46	(-0.65	to -0.27)	<0.001
X-ray severity for women				
1 or 2	Reference			
3	-0.04	(-0.14	to 0.07)	0.470
4	-0.29	(-0.39	to -0.18)	<0.001
Sex, women	-0.56	(-0.67	to -0.46)	<0.001
Multivariable-adjusted model ^b				
X-ray severity for men				
1 or 2	Reference			
3	-0.26	(-0.46	to -0.07)	0.007
4	-0.37	(-0.55	to -0.20)	<0.001
X-ray severity for women				
1 or 2	reference			
3	0.00	(-0.09	to 0.09)	0.980
4	-0.18	(-0.27	to -0.09)	<0.001
Age, per 10 years	-0.41	(-0.46	to -0.36)	<0.001
Sex, women	-0.71	(-0.89	to -0.53)	<0.001
Total fat mass, per kg	0.00	(-0.00	to 0.01)	0.329

Analysis of 2172 limbs among 1093 knee osteoarthritis patients

^a General linear model adjusted for sex with consideration for intra-individual correlation using cluster variance. The adjusted mean difference slightly differed by sex, although sex was not shown to modify the association between KOA severity and phase angle (P for interaction = 0.073)

Bold font indicates significance at $P < 0.05$ in P value column

^b General linear model adjusted for age, sex, and fat mass with consideration for intra-individual correlation using cluster variance. The adjusted mean difference was differed by sex because sex modified the association between KOA severity and phase angle (P for interaction = 0.048)

KOA knee osteoarthritis, CI confidence interval

severity-specific or sex-specific differences in the association between PhA and quadriceps strength are described in Supplementary Text 1. Interactions were assessed with the Wald test. A p value < 0.05 was considered to indicate statistical significance.

Results

Patient flow and descriptive statistics

Initially, 1217 patients with KOA who met the inclusion criteria were identified. Of these, 69 patients without the new KSS data, KOA severity category data, or diabetes were excluded. After further excluding patients with missing exposure and outcome variables for analyses, 1093 patients were

included in the analyses (Fig. 2). Table 1 summarizes the baseline characteristics of the study population. The mean age was 72.8 years (standard deviation, 8.0 years), and more than three quarters (78%) of the patients were women.

KOA severity and PhA per leg

Table 2 shows the association between KOA severity and PhA. Evidence of a sex-specific difference in the association between KOA severity and PhA was found ($P = 0.073$ for interaction and 0.048 for sex- and multivariable-adjusted models, respectively). We found statistically significant relationships between increasing KOA severity and decreasing PhA in men, as shown in Table 2 (grade 4 KOA, mean difference = -0.26° , 95% confidence interval (CI) = -0.46 to -0.07° and grade 3 KOA, mean difference = -0.37° , 95% CI = -0.55 to -0.20°). In

Table 3 Associations between phase angle and quadriceps strength^a

Quadriceps strength per limb, Nm	Mean difference	(95% CI)		P value
PhA, per 1 degree	7.54	(5.51	to 9.57)	< 0.001
Age, per 10 years	− 1.30	(− 3.23	to 0.63)	0.186
Sex, female	− 11.82	(− 17.99	to − 5.65)	< 0.001
Diabetes, yes	− 0.61	(− 4.84	to 3.61)	0.776
Total fat mass, kg	− 0.07	(− 0.25	to 0.10)	0.414
KSS per limb, point	− 1.46	(− 1.79	to − 1.13)	< 0.001
Lower limb muscle mass per limb, kg ^b				
With x-ray grade 1 or 2	8.50	(6.53	to 10.47)	< 0.001
With x-ray grade 3	5.45	(2.62	to 8.27)	< 0.001
With x-ray grade 4	4.79	(2.07	to 7.51)	0.001

Analysis of 2172 limbs among 1093 knee osteoarthritis patients

^a General linear model adjusted for age, sex, diabetes, fat mass, pain score, and x-ray grade with consideration for intra-individual correlation using cluster variance. The adjusted mean difference did not differ by KOA severity or sex because neither KOA severity nor sex modified the association between PhA and quadriceps strength (*P* for interaction = 0.185 and 0.133 for KOA severity and sex, respectively)

^b Within each KOA grade subcategory, the adjusted mean differences are estimated because KOA modified the association between lower limb muscle mass and quadriceps strength in our previous study

Bold font indicates significance at *P* < 0.05 in *P* value column

KOA knee osteoarthritis, CI confidence interval, PhA phase angle

women, only KOA grade 4 was significantly associated with a decrease in PhA, and its magnitude is smaller than that in men (Table 2: mean difference = − 0.18°, 95% CI = − 0.27 to − 0.09°). Women also had smaller PhAs than men (Table 2: mean difference = − 0.71°, 95% CI = − 0.89 to − 0.53°). Figure 3 shows the adjusted mean PhA values by KOA severity for each sex; those with grade 4 disease had the lowest PhA values in both sexes (PhA at grade 4 was 4.29° (95% CI = 4.19 to 4.39°) and 3.77° (95% CI = 3.72 to 3.81°) in men and women, respectively).

PhA and quadriceps strength per leg

Table 3 shows the associations between PhA and quadriceps strength. Evidence of a difference in the association between PhA and quadriceps strength was not found for KOA severity and sex (*P* for interaction = 0.185 and 0.133 for KOA severity and sex, respectively). Therefore, analyses were performed without considering the interaction terms. PhA per leg was positively associated with quadriceps strength per leg independent of age, sex, leg muscle mass, pain, and KOA severity (Table 3: mean difference per 1° increase = 7.54 Nm (95% CI = 5.51 to 9.57 Nm). Figure 4 shows the adjusted mean quadriceps strength by PhA per leg. For example, patients who had a PhA of 2° per leg had a quadriceps strength of 35.9 Nm on average (95% CI = 30.0 to 41.9 Nm), whereas those who had a PhA of 7° per leg had a quadriceps strength of 73.6 Nm on average (95% CI = 69.2 to 78.1 Nm).

Discussion

Our results showed that PhA gradually decreased with increasing KOA severity, and this association was similar in both sexes. In addition, PhA was positively associated with quadriceps strength regardless of KOA severity. These findings may encourage clinicians to pay more attention to PhA to improve quadriceps function in patients with KOA.

Several explanations are possible for the association of lower PhA with KOA progression. First, it can be explained in part by the decrease in muscle mass as KOA progresses [17]. PhA in part reflects the amount and quality of soft tissue, such as muscle and fat, and a previous study has shown that decreases in PhA were associated with loss of muscle mass, whereas increases in PhA were associated with increased fat mass [5]. Second, low PhA in patients with KOA can be explained by alteration in the cells and molecules of the quadriceps muscle. A previous study has shown that the quadriceps muscle in patients with KOA is characterized by excessive extracellular matrix, fewer satellite cells, and greater collagen content than in patients without KOA [18].

PhA was higher among male patients with KOA than among their female counterparts, which is in accordance with the results of previous studies [3, 7]. However, the association between PhA and KOA severity differed with sex. The reason for the sex-specific difference in the association is not known; however, it can be attributed to the differing amount and quality of muscle and fat and alteration in the cells and molecules of the quadriceps muscle in both sexes.

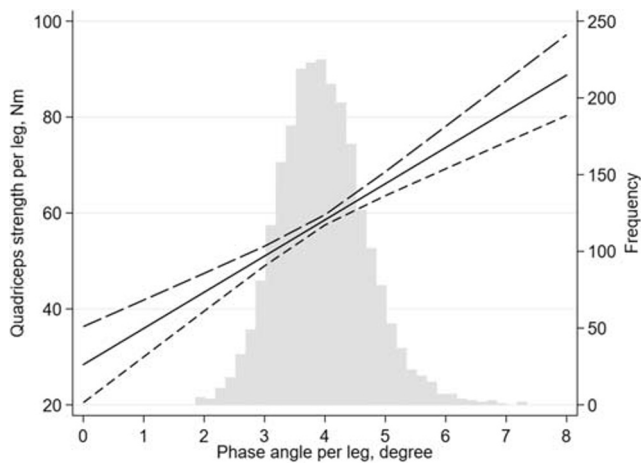


Fig. 4 Predicted quadriceps strength by phase angle per leg. Using the multivariable-adjusted general linear model including age, sex, diabetes, fat mass, pain score, leg muscle mass, x-ray grade, and interaction pairs (the product terms of leg muscle mass and x-ray grade), adjusted mean quadriceps strength by phase angle per leg was predicted. The left vertical axis shows adjusted mean quadriceps strength. The solid line indicates the predicted point estimates of quadriceps strength. The dotted lines indicate 95% confidence intervals. Gray bars indicate frequency at which the phase angle values were measured. The right vertical axis shows frequency of each gray bar

We believe that the demonstrated association of increasing PhA with increasing quadriceps strength has several implications for researchers and clinicians. First, the observed association is independent of lower limb muscle mass. Quadriceps strength may be decreased by alterations in cellular and molecular properties, which, in turn, may be reflected by the decreased PhA value, as PhA is generally reflective of cell membrane integrity and cell function [4, 5, 19]. Second, PhA may be modified through short-term resistance training [20, 21]. Thus, resistance training may be effective in improving PhA among patients with less severe KOA. Conversely, in patients with advanced KOA, for whom resistance training may be unfeasible because of knee pain, suspension training may promote PhA increase [22] by modulating exercise intensity, thereby controlling knee pain during weight-bearing exercise. Further research is required to determine whether these interventions are effective in improving PhA in patients with KOA.

Our study has several strengths. First, we analyzed both limbs in each patient using a suitable statistical method. Accordingly, our findings can be applied to both limbs in a single patient with KOA, given that osteoarthritis often affects both knees; this is supported by our finding that 95% of the non-surgical sides had grade 3/4 KOA. Second, PhA values are expected to be similar regardless of the BIA instruments used or their manufacturers: this is because PhA is directly derived from reactance and resistance values via a uniform, simple mathematical transformation.

Several limitations are also acknowledged in this study. First, the cross-sectional design did not allow investigation of the causal relationships between PhA and KOA severity and quadriceps strength. Second, the participants in this study were not representative of patients with KOA because most of them had severe KOA and were awaiting knee replacement surgery. However, we believe that the association between PhA and KOA severity and quadriceps strength is a valuable finding that should be validated in patients with KOA who do not require surgical treatment.

In conclusion, our study showed that PhA gradually decreased with increasing KOA severity, especially in men. In addition, the association of increasing PhA with increasing quadriceps strength was found regardless of KOA severity. To create a better program for improving quadriceps function in patients with KOA, clinicians should focus on increasing both muscle mass and PhA.

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Availability of data and material The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors' contributions Research idea and study design: OW, NK; data acquisition: OW, KM; data analysis and interpretation: OW, NK, MY, KM; statistical analysis: NK; supervision or mentorship: NK, MY, KM. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Disclosures None.

Ethical approval The study was approved by the local institutional review board (no. 57, January 26, 2017) and by the Research Ethics Committee of Fukushima Medical University School of Medicine (no. 2850, September 28, 2016).

Consent to participate Informed consent for the present study was not mandatory according to the “ethical guidelines for medical and health research involving human subjects” in Japan.

Consent for publication Not applicable

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