

Increase in echo intensity and extracellular-to-intracellular water ratio is independently associated with muscle weakness in elderly women

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Received: 12 February 2017 / Accepted: 18 July 2017 / Published online: 28 July 2017
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Abstract

Purpose The changes in muscle composition and its heterogeneity during aging are associated with muscle weakness in elderly persons independent of decreases in muscle mass or muscle thickness (MT). Both the assessment of echo intensity (EI) with ultrasound imaging and the evaluation of the extracellular water/intracellular water (ECW/ICW) ratio with segmental bioelectrical impedance spectroscopy (BIS) are non-invasive and convenient methods and seem valuable for muscle quality determination. However, no previous study has evaluated both EI and the ECW/

ICW ratio simultaneously to investigate their relationship to muscle strength. The purpose of the present study was to investigate whether both EI and the ECW/ICW ratio are independently associated with muscle strength in elderly women.

Methods A total of 179 elderly women with a mean age of 74.1 ± 4.9 years, living independently in the community, were enrolled. The MT and EI of the quadriceps femoris were measured using transverse ultrasound imaging. The ECW/ICW ratio in the upper thigh was calculated from segmental BIS. The maximum knee extensor strength and the presence of knee pain were also assessed.

Results Knee extensor strength showed a significant positive correlation with MT, and significant negative correlations with EI, the ECW/ICW ratio, and age. Stepwise regression analysis revealed that knee extensor strength in elderly women was predicted by MT, EI, and the ECW/ICW ratio.

Conclusions This study suggests that the simultaneous application of EI and the ECW/ICW ratio is useful in assessing muscle strength, and accurately estimates the changes in muscle quality related to muscle weakness.

Keywords Muscle strength · Muscle quality · Echo intensity · Extracellular water · Muscle thickness

Communicated by Nicolas Place.

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Abbreviations

BIS	Bioelectrical impedance spectroscopy
BMI	Body mass index
ECW	Extracellular water
EI	Echo intensity
ICW	Intracellular water
MT	Muscle thickness
RF	Rectus femoris
VI	Vastus intermedius

Introduction

Sarcopenia was first described as a decrease in skeletal muscle mass associated with aging (Rosenberg 1997), and widely considered in recent years to be a progressive decline in skeletal muscle mass and increased weakness coinciding with advancing age (Cruz-Jentoft et al. 2010). In association with the decrease in skeletal muscle mass and power that accompanies aging (Rice and Keogh 2009; Reid et al. 2014), muscle strength in elderly people aged 65 years and older is reduced by 1–2% per year (Skelton et al. 1994). The decline of muscle strength in the lower extremities is greater than that in the upper extremities (Janssen et al. 2000); thus, the weakness of the knee extensors plays a significant role in the future decline of walking ability (Rantanen et al. 2001). Therefore, assessment of muscle strength in the lower extremities is important for elderly people.

In addition to the change in muscle quantity, muscle composition also changes with aging, including increasing adipose tissue accumulation, change of the water content distribution within skeletal muscle, fibrosis, change in electrical properties, and change of the extracellular matrix (Goodpaster et al. 2001; Sipila et al. 2004; Yamada et al. 2010, 2016a).

Imaging modalities such as magnetic resonance imaging, computed tomography, and dual-energy X-ray absorptiometry are considered the gold standard methods for assessing muscle quantity. In addition, muscle quality can be evaluated by measuring the ratio of non-contractile tissue to contractile tissue through modern techniques (Kent-Braun et al. 2000; Azzabou et al. 2015). However, these measurements need expensive and large equipment. In contrast, echo intensity (EI) measurement with ultrasound imaging is a non-invasive and convenient method of muscle quality assessment and has been used in many recent studies (Cadore et al. 2012; Radaelli et al. 2012; Rech et al. 2014). Enhanced EI is associated with increasing intramuscular adipose and fibrous tissue (Heckmatt et al. 1982; Reimers et al. 1993; Pillen et al. 2009), and represents changes in muscle quality. Muscle quantity [i.e. muscle thickness (MT)] assessed with ultrasound imaging and EI were independently associated with knee extensor strength in middle-aged and elderly persons (Fukumoto et al. 2012b); thus, EI was found to be an important parameter that affects muscle strength.

Recently, segmental bioelectrical impedance spectroscopy (BIS), another non-invasive and convenient method of muscle quality assessment, has been developed (Yamada et al. 2014). Skeletal muscle tissue has a large amount of water, and segmental BIS can separately assess intracellular water (ICW) and extracellular water (ECW), which are divided by the muscle cell membrane. Segmental BIS can

distinguish ICW and ECW from the total water in a particular segment. In comparison with the general whole-body bioelectrical impedance analysis method, segmental BIS is advantageous for assessments of a localized region and has a theoretically high degree of accuracy according to the principle of the Cole–Cole model (Yamada et al. 2013). ICW reflects muscle cell mass, whereas ECW represents the sum of interstitial fluid and blood plasma in extracellular space. A previous study (Yamada et al. 2016b) had confirmed the ECW/ICW ratio as a measure of muscle quality. As the calculations of ICW and ECW are affected by segmental volume, the ECW/ICW ratio could indicate the ratio of non-contractile tissue to contractile tissue regardless of somatotype. Thus, a high ECW/ICW ratio is indicative of the relative increase of non-contractile tissue and associated with the loss of knee extensor strength (Yamada et al. 2016b).

Both ultrasonography and segmental BIS are non-invasive and convenient, and thus very attractive methods in the clinical setting. However, to the best of our knowledge, no previous study has evaluated whether both EI and the ECW/ICW ratio are independently related to muscle strength. EI and the ECW/ICW ratio represent different qualitative changes in muscle; enhanced EI represents increased intramuscular adipose and fibrous tissue, whereas the ECW/ICW ratio represents the relative increase of fluid in extracellular space. Therefore, we hypothesized that the increase of both parameters is independently associated with the loss of muscle strength. The purpose of the present study was to investigate whether both EI and the ECW/ICW ratio are independently related to muscle strength in elderly women.

Methods

Participants

A total of 179 elderly women with a mean age of 74.1 ± 4.9 years (range 65–89 years), living independently in the community, were enrolled in the present study. The study protocol was approved by the ethics committee of Kyoto Gakuen University. Written informed consent was obtained from all participants.

The inclusion criteria were as follows: (a) reported ability to walk without a cane, (b) no history of lower-limb trauma or surgery, (c) no neuromuscular disorder, (d) no current medication for oedema or no use of an artificial pacemaker, (e) no acute disease that causes muscle weakness, (f) no definitive kidney or digestive disorder, and (g) ability to provide informed consent without severe dementia.

Table 1 Physical characteristics and muscle strength, quantity, and quality of the participants ($n = 179$)

	Mean $\pm$ SD
Physical characteristics	
Age (years)	74.1 $\pm$ 4.9
Height (cm)	151.9 $\pm$ 5.0
Weight (kg)	50.0 $\pm$ 7.2
Body mass index (kg/m ²)	21.7 $\pm$ 2.8
Knee pain (n ; %)	48 (27%)
Knee extensor strength (Nm)	92.5 $\pm$ 26.6
Muscle thickness (cm)	3.2 $\pm$ 0.6
Echo intensity	97.0 $\pm$ 10.8
ECW/ICW ratio	0.75 $\pm$ 0.23

SD standard deviation, ECW/ICW ratio extracellular water/intracellular water ratio

Height and body weight were measured to the nearest 0.1 cm and 0.1 kg with the subjects standing and wearing light workout clothing without shoes. Body mass index (BMI) was then calculated. The anthropometric characteristics of the participants are shown in Table 1.

The experimental procedure was unified among all subjects to control the influence of the immediate effect; after the participants had lain in the supine position, we performed ultrasound image measurements followed by segmental BIS measurements.

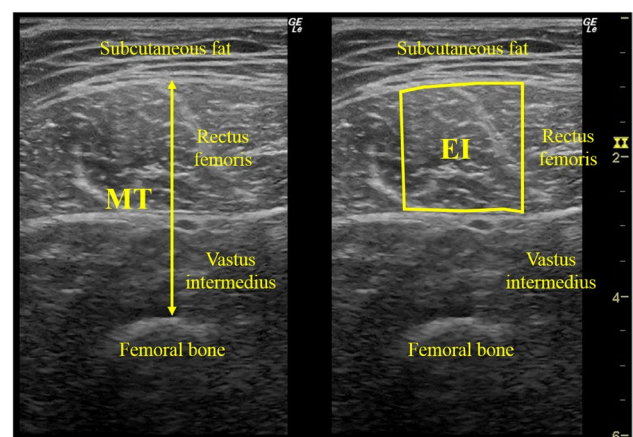
Ultrasound measurement

The participants were instructed to lie in the supine position and relax completely. Measurements from the ultrasound images were taken after the participants had lain in the supine position for approximately 3 min. The rectus femoris (RF) and vastus intermedius (VI) muscles within the quadriceps femoris on the right lower extremity were investigated. Transverse ultrasound images were obtained using a B-mode ultrasound device with an 8-MHz linear transducer (LOGIQ e; GE Healthcare UK Ltd., Chalfont, UK). In accordance with a previous study (Fukumoto et al. 2012b), the transducer was set perpendicular to the longitudinal axis of the quadriceps femoris, as the sum of the RF and VI muscles at the midpoint between the anterior superior iliac spine and the proximal end of the patella. B-mode ultrasonography with a unified dynamic range of 69 Hz and a 58-dB gain was used, with the same examiner performing all measurements. Dynamic focus depth was set to the middle of the RF muscle in each subject. The head of the probe was covered with a water-soluble transmission gel for acoustic coupling, and the pressure of the transducer was kept to a minimum.

The measurement of MT and EI are shown in Fig. 1. The sum of the RF and VI thicknesses was measured as the distance of the well-demarcated zone between the lower boundary of the ventral fascia of the RF and the upper margin of the femoral bone. EI was investigated by means of 8-bit grayscale analysis with Image J-WinJP (LISIT, Tokyo, Japan) in accordance with a previous study (Taniguchi et al. 2015). Regions of interest were determined as the specific area of the RF muscle avoiding the surrounding fascia and within the width of the femoral bone. The EI of the regions of interest was presented on a 256-point scale from 0 to 255, and the average EI was calculated using two measurements from the same transverse image. Previous studies (Fukumoto et al. 2012b; Taniguchi et al. 2015) have shown the test–retest reliabilities of the ultrasound technique for measuring MT and EI.

Bioelectrical impedance spectroscopy

The participants were laid down in a supine position, and their arms and legs were relaxed and slightly abducted. Segmental BIS was performed for a logarithmic spectrum of 140 frequencies ranging from 2.5 to 350 kHz (MLT-550; SK Medical, Shiga, Japan) using disposable electrodes (42.5 $\times$ 38 mm, Blue-sensor SP-00-S; Mets Inc., Tokyo, Japan), as previously described (Yamada et al. 2010). Segmental BIS measurements of the right upper thigh were performed 3–5 min after the participants had lain in the supine position to avoid the immediate effect of the transition from a standing to a supine position and the subsequent shift in body fluids from the lower extremities to the trunk (Kushner et al. 1996). Thus, segmental BIS was conducted after muscle ultrasonography measurements. After electrode sites were cleaned with alcohol, disposable electrodes were applied over the four sites on the right side of the

**Fig. 1** Measurement of muscle thickness (MT) and echo intensity (EI)

body according to a previous study (Yamada et al. 2014). Two current-carrying electrodes were placed on the dorsal surfaces of the hand and foot. Two sensing electrodes were placed on the anterior superior iliac spine and lateral knee articular condyles. For segmental BIS measurements, segmental length was measured as distance between the two sensing electrodes. Segmental BIS measurements were taken for approximately 15 s for a sweep of frequencies and performed for three consecutive repetitions.

Data processing was performed using the software supplied with the BIS equipment. The results of segmental BIS, representing the resistance of the ECW compartment ($R_{ECW} = R_0$) and the ICW compartment ($R_{ICW} = 1/[1/R_\infty - 1/R_0]$), were identified by fitting the spectrum of bio-impedance data to the Cole–Cole model. R represents the resistance. According to the algorithm used in previous studies (Zhu et al. 1998; Kaysen et al. 2005; Yamada et al. 2013), the analysis parameters were as follows: $ECW = \rho_{ECW} \times \text{length}^2/R_\infty$ and $ICW = \rho_{ICW} \times \text{length}^2/R_{ICW}$, where ρ represents the factors for extracellular ($\rho_{ECW} = 47 \Omega\text{m}$) and intracellular ($\rho_{ICW} = 273.9 \Omega\text{m}$) resistivity. The mean values obtained in the three repetitions were determined for subsequent analysis, and the ECW/ICW ratio was calculated in the upper thigh segment.

Muscle strength and knee pain measurement

The maximum knee extensor strength test was performed in the following order: the participants were seated on an isometric dynamometer (TKK5710e; Takei Scientific Instruments, Niigata, Japan) with a knee flexion angle of 90° and the feet off the floor. The sensor pads were positioned on the leg just proximal to the ankle joint. After familiarization with the knee extensor strength test, the participants were instructed to perform maximal effort of isometric knee extension. Verbal encouragement was provided to motivate the subjects to produce their maximal effort. The knee extensor strength was measured twice for 3 s, and

the highest value (N) was obtained. Each strength value was converted into knee extensor torque (Nm) by multiplying with the lever arm length (m). In addition, the presence of knee pain during walking within the past month was assessed because knee pain is a common symptom among the elderly (Helme and Gibson 2001) and could affect the generation of knee extensor strength (Liikavainio et al. 2008; Scott et al. 2012).

Statistical analysis

All data are expressed as mean $\pm$ standard deviation. All statistical analyses were performed with SPSS software (SPSS Statistics version 22.0; SPSS Japan Inc., Tokyo, Japan). The level of significance was set at $p < 0.05$. Correlations between knee extensor strength, MT, EI, the ECW/ICW ratio, and physical characteristics (age and BMI) were calculated using Pearson's correlation coefficients.

A multiple linear regression analysis with the stepwise method was performed to identify the predictors associated with knee extensor strength as a dependent variable. In the linear model, age, BMI, the presence of knee pain, MT, and EI were entered as candidate variables in model 1, and the ECW/ICW ratio was entered in model 2, to estimate the contribution of the ECW/ICW ratio to muscle strength. The variance inflation factor values were calculated to confirm the presence of a multicollinearity effect.

Results

The physical characteristics of the participants and their muscle strength, quantity, and quality are presented in Table 1. The correlation coefficients between muscle strength, quantity, quality, and physical characteristics of the participants are presented in Table 2. Knee extensor strength showed a significant positive correlation with MT ($p < 0.001$) and a significant negative correlation with EI ($p < 0.001$), the ECW/ICW ratio ($p < 0.001$), and age

Table 2 Correlation coefficients between muscle strength, quantity, quality, and physical characteristics of the participants ($n = 179$)

	Knee extensor strength	Muscle thickness	Echo intensity	ECW/ICW ratio	Age	BMI
Knee extensor strength	–	0.382*	–0.320*	–0.334*	–0.226*	0.123
Muscle thickness		–	–0.498*	–0.275*	–0.336*	0.272*
Echo intensity			–	0.190*	0.154*	0.009
ECW/ICW ratio				–	0.279*	–0.112
Age					–	–0.129*
BMI						–

ECW/ICW ratio extracellular water/intracellular water ratio, BMI body mass index

Statistical significance: * $p < 0.05$, ** $p < 0.01$

($p = 0.001$). There was also a significant positive correlation between EI and the ECW/ICW ratio ($p = 0.006$). Stepwise regression analysis in model 1 indicated that MT and EI were significantly associated with knee extensor strength. The ECW/ICW ratio was selected as a significant variable in addition to those variables for knee extensor strength (Table 3). The variance inflation factors ranged from 1.086 to 1.393 in model 2, confirming a multicollinearity effect.

Discussion

To the best of our knowledge, the present study is the first to evaluate both EI and the ECW/ICW ratio simultaneously as muscle quality indices and to investigate their relationship with muscle strength in the elderly. In accordance with a previous study (Fukumoto et al. 2012b), the first model showed that MT and EI were independently associated with muscle strength. In the second model, the ECW/ICW ratio was added as an independent variable and EI remained as an independent variable significantly associated with muscle strength; thus, the association of EI and muscle strength was not influenced by the ECW/ICW ratio. Notably, the ECW/ICW ratio also significantly contributed to muscle strength in the second model. These results, namely both enhanced EI and high ECW/ICW ratio which indicate muscle quality, were independently associated with the loss of muscle strength in elderly women, supported our hypothesis. This study suggests that the simultaneous assessment of EI and the ECW/ICW ratio can accurately estimate the changes in muscle quality.

A previous study (Kent-Braun et al. 2000) considered changes in muscle quality as the product of a relative increase of non-contractile tissue within the muscle, which is ultimately related to muscle weakness. Enhanced EI is caused by the infiltration of fat and fibrous tissue between muscle fibers (muscle cells), increasing the

interface with heterogeneous tissue (Reimers et al. 1993; Pillen et al. 2009; Goodpaster et al. 2001). Recently, however, Akima et al. (2016) reported that EI showed no significant correlation with intramyocellular lipids but rather with extramyocellular lipids. Therefore, EI is assumed to reflect the abundance of non-contractile tissue in the extramyocellular space. Additionally, fat and fibrous tissues appear white on ultrasound images, whereas water and fluid appear black. Thus, enhanced EI was assumed to be unrelated to water content. Currently, there is no physiological evidence to prove that EI reflects the ECW in the extramyocellular space. However, as fat and fibrous tissue have high impedance values, ECW measured with segmental BIS represents both the water content in the extracellular space and fat and fibrous tissue. The present study showed a weak but significant positive correlation between EI and the ECW/ICW ratio. An increased ECW/ICW ratio was considered to include both the relative increase in non-contractile tissue and the water content in extracellular space. However, in the results of multiple regression analysis, both EI and the ECW/ICW ratio were found to be independent variables that influence muscle strength in elderly women. The standardized regression coefficients of EI were decreased from model 1 to model 2 in the multiple regression analysis. There is a possibility that the result subtracts the influence of mutually overlapping portions of the contribution ratio in muscle strength, as EI and the ECW/ICW ratio are not completely independent. These results suggest that the simultaneous application of EI and the ECW/ICW ratio can be used complementarily to evaluate qualitative changes in muscle that cannot be evaluated individually. Taken together, EI and the ECW/ICW ratio represent mostly different aspects of qualitative changes in muscle, EI reflects fat and fibrous tissue in extracellular space and the ECW/ICW ratio reflects the water content in extracellular space.

The assessment of body composition and ultrasound images vary with age and disease. A previous study

Table 3 Predictors of muscle strength in elderly women ($n = 179$)

Dependent variables	Independent variables	Coefficient	Standardized coefficient	p value	95% confidence interval
Model 1					
$R^2 = 0.17$	Muscle thickness	12.70	0.30	<0.01	[5.98, 19.41]
	Echo intensity	−0.42	−0.17	0.03	[−0.81, −0.04]
Model 2					
$R^2 = 0.22$	Muscle thickness	10.23	0.24	<0.01	[3.56, 16.90]
	Echo intensity	−0.38	−0.16	0.04	[−0.76, −0.01]
	ECW/ICW ratio	−27.09	−0.24	<0.01	[−42.64, −11.53]

R^2 represents the coefficient of determination

ECW/ICW ratio extracellular water/intracellular water ratio

(Hirani et al. 2016) suggested that changes in body composition such as low muscle mass and sarcopenic obesity were associated with poor functional outcomes. Another study (Yamada et al. 2014) also reported that elderly persons requiring care had a relative increase in the ECW in the legs. Therefore, assessment of body composition would be useful in estimating physical function related to aging and sarcopenia in addition to muscle strength. Ultrasound images were assessed for hip and knee osteoarthritis, and previous studies (Fukumoto et al. 2012a; Taniguchi et al. 2015) showed that patients with painful osteoarthritis had changes in muscle quantity and quality. The results of the present study showed that knee pain was not independently associated with muscle strength although 27% of the participants had knee pain. Knee pain in the elderly is often caused by knee osteoarthritis (Yoshimura et al. 2009), and it is possible that the present study also included patients with knee osteoarthritis. Taniguchi et al. (2015) reported that patients with knee osteoarthritis had decreased MT and enhanced EI compared with healthy controls. Other previous studies (Rice and Keogh 2009; Reid et al. 2014) showed that neuromuscular activation deficits, such as loss of muscle power, precede changes in muscle properties and strength. Although the present study investigated the relationship between muscle strength and muscle quality by focusing on EI and the ECW/ICW ratio, further studies on neurological factors that affect muscle strength (Klein et al. 2001; Oliviero et al. 2006) are needed.

This study has some limitations. First, the setting conditions before measurements of EI and the ECW/ICW ratio may have been insufficient. To avoid an immediate effect of the transition, these measurements are recommended to be performed at least 10–15 min after the participants had lain in the supine position with restricted water intake. In the present study, the measurement procedures were unified after the participants had lain in the supine position; therefore, the influence of the immediate effect was maximally controlled. Second, the present study used the EI of the RF as a representative of the total quadriceps EI. Although the EI of the individual quadriceps muscles indicated a significant negative correlation (Wilhelm et al. 2014), the EI of the total quadriceps was the strongest contributor to functional performance (Lopez et al. 2017). Finally, although the sample size in the present study was large enough, the participants were exclusively healthy elderly women. Therefore, our results may not be applicable to other populations such as the young or elderly men. Further studies are needed to clarify whether the results of the present study are generalizable to other populations.

Conclusions

This study showed that enhanced EI and a high ECW/ICW ratio were independently associated with loss of muscle strength in elderly women. To the best of our knowledge, this is the first study to demonstrate the simultaneous application of MT and EI measured with ultrasonography, and the ECW/ICW ratio measured with segmental BIS to assess the changes in muscle quality related to muscle weakness in the elderly. Ultrasound imaging and segmental BIS are non-invasive and convenient tools for assessing muscle quality, and therefore are expected to be useful for establishing methods of muscle quality assessment for preventing sarcopenia.

Acknowledgements The authors would like to thank Nishimura T, Watanabe A, Kaihara C, Iwane K, and Shoji Y for their practical and technical assistance. The authors also thank all individuals who participated in the study. This study was not funded by any institutions, agencies, or companies.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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