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Original Article

The Impact of Reduced Skeletal Muscle Mass on Patients with Knee Osteoarthritis

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Although several studies have suggested a possible association between sarcopenia and knee osteoarthritis (OA) in the elderly, there remains no definitive evidence. Recently, however, the serum creatinine/cystatin C ratio (sarcopenia index: SI) was reported to correlate with skeletal muscle mass. The present retrospective study therefore investigated the impact of reduced skeletal muscle mass on advanced knee OA using SI. In 55 individuals scheduled for knee osteotomy or knee arthroplasty, correlations between SI and patient-reported outcomes such as the Knee Society Score (KSS), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Oxford Knee Score (OKS) were explored. Significant associations were found between SI and the KSS functional activity score ($\beta = 0.37$; $p = 0.022$), KOOS subscale for activities of daily living ($\beta = 0.42$; $p = 0.0096$), and OKS ($\beta = 0.42$; $p = 0.0095$). This study underscores the role of reduced muscle mass in functional outcomes and introduces SI as a valuable marker for assessing muscle loss in knee OA patients.

Key words: knee osteoarthritis, sarcopenia index, reduced muscle mass, activities of daily living, functional activity

The aging of populations is a growing, global-scale problem. In aging societies, the incidence of age-related diseases increases and threatens the health of the elderly population. Sarcopenia, the most common age-related disease, is defined as a decrease in skeletal muscle mass and muscle strength or physical function [1]. The prevalence of sarcopenia varies depending on the population and definition, but results from large studies have estimated the prevalence in the general population as 6-12% [2]. Elderly patients with sarcopenia experience greater risks of falls, fractures, and frailty [2], leading to functional disability and decreased activities of daily living (ADL). In addition, the possible association between osteoarthritis (OA), another age-related disease, and sarcopenia is often discussed. And although several reports have suggested an association between sarcopenia and OA [3-6], solid evidence has been lacking and the relationship remains unclear [7, 8].

In many hospitals, diagnosis of sarcopenia is made difficult by lack of access to whole-body dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). On this issue, the Asian Working Group for Sarcopenia in 2019 recommended diagnostic use of the term "possible sarcopenia" in primary healthcare settings without advanced diagnostic equipment, and promotion of lifestyle interventions and health education for patients with this tentative diagnosis [9]. However, use of the condition "possible sarcopenia" is

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generally not recommended in hospital and research settings, and sarcopenia remains somewhat difficult to diagnose.

The sarcopenia index (SI), defined as the ratio of serum creatinine to serum cystatin, has recently been reported as a surrogate marker for skeletal muscle mass [10,11]. SI is a non-invasive, inexpensive objective measure for estimating muscle mass. A previous report has shown that SI correlates with both muscle mass and physical function [12]. In addition, SI appears to correlate with each of the component criteria for sarcopenia [13]. SI is thus expected to serve as a useful marker for the simple assessment of sarcopenia without advanced measuring equipment. If SI facilitates a more accurate estimation of the incidence of sarcopenia, the relationship between OA and sarcopenia may become clear, and the challenges faced by elderly patients with both sarcopenia and advanced OA could come into better focus. The purpose of the present study was thus to evaluate the effect of skeletal muscle mass loss on patients with knee OA using SI.

Materials and Methods

Patient selection. This retrospective, single-center study enrolled 82 consecutive patients with advanced knee OA who underwent either osteotomy around the knee or total/unicompartmental knee arthroplasty between April 2020 and January 2023. To avoid the influence of chronic kidney disease or other conditions that cause muscle atrophy, the exclusion criteria included estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, inflammatory diseases such as rheumatoid arthritis, or surgery requiring general anesthesia for trauma or other diseases within the preceding year. This study was approved by the local ethics committee (No. 21-025, 23-022). All patients provided written informed consent.

Evaluations. We assessed the preoperative status of patients, including age, sex, body mass index (BMI), visual analogue scale (VAS), range of motion, Kellgren–Lawrence grade (K–L), SI, and patient-reported outcomes (PROs). The evaluated PROs were the Knee Society Score (KSS), Knee injury Osteoarthritis Outcome Score (KOOS), and Oxford Knee Score (OKS). SI was calculated as (serum creatinine/cystatin C) $\times 100$ according to a previous report [11].

Statistical analysis. The primary outcome of the study was the association between each PRO and skeletal muscle mass as estimated by SI. Multiple regression analysis was used for the analysis of associations. Each PRO subscale was considered a dependent variable. Age, sex, and BMI were included as independent variables in addition to SI. All statistical analyses were performed using EZR software [14]. *Post hoc* statistical power was calculated by the program G*Power (version 3.1.9.7), with a setting of $\alpha = 0.05$. All data are shown as mean ± standard deviation, with values of $p < 0.05$ considered significant. Results are shown with the standardized partial regression coefficient (β), 95% confidence intervals (CIs), and *p*-values. Data were accessed for research purposes between December 2020 and November 2023.

Results

Patient characteristics. After applying the exclusion criteria, 55 patients (55 knees) were included. The patient characteristics are summarized in Table 1.

Primary outcome. For the primary outcome, the association between each PRO and SI was statistically analyzed using multiple regression analysis. No multicollinearity was evident in the independent variables, which had variance inflation factors of 1.08 (age), 1.04 (BMI), 1.81 (sex), and 1.91 (SI). Among the PRO subscales, the KSS functional activity score ($\beta = 0.37$, 95%CI = 0.06-0.68; $p = 0.022$), KOOS ADL ($\beta = 0.42$, 95%CI = 0.11-0.73; $p = 0.0096$), and OKS ($\beta = 0.42$, 95%CI = 0.11-0.73; $p = 0.0095$) were found to be significantly associated with SI (Table 2).

Post hoc power analysis. Statistical power (1-β) as analyzed by G*Power was 0.99 for each of KSS functional activity, KOOS ADL, and OKS.

Discussion

The most important finding of our study was the clear association between skeletal muscle mass, as estimated by SI, and various functional outcomes in patients with knee OA. Reduced muscle mass was linked to poorer functional outcomes. Specifically, both the functional activity score of the KSS and the ADL subscale of the KOOS exhibited positive correlations with muscle mass. Additionally, the OKS also demonstrated a positive association with muscle mass.

Table 1 Patient characteristics

Age (years)		72.7 ± 8.1
BMI (kg/m^2)		25.1 ± 3.2
Sex (male : female)		20 : 35
Extension (°)		−6.5 ± 7.2
Flexion (°)		128.6 ± 14.1
VAS (mm)		66.7 ± 25.3
Sarcopenia Index		80.8 ± 14.4
Kellgren-Lawrence grade (n)	2	9
	3	12
	4	34
KSS	Objective score (/100)	39.3 ± 23.4
	Satisfaction (/40)	10.7 ± 4.9
	Expectations (/15)	13.1 ± 2.0
	Functional activities (/100)	43.8 ± 18.5
KOOS	Symptom (/100)	53.9 ± 17.9
	Pain (/100)	41.3 ± 16.6
	ADL (/100)	52.3 ± 18.1
	Sports/Recreation (/100)	17.6 ± 17.4
	QOL (/100)	24.5 ± 16.1
OKS (/48)		23.0 ± 8.2

BMI, body mass index; VAS, visual analogue scale; KSS, Knee Society Score; KOOS, Knee injury Osteoarthritis Outcome Score; OKS, Oxford Knee Score.

Table 2 Adjusted regression analysis of the associations between each PRO subscale and SI

		R^2	β	95%CI	*P*-value
KSS	Objective score	0.30	0.19	−0.14 to 0.53	0.25
	Satisfaction	0.05	0.03	−0.36 to 0.42	0.88
	Expectations	0.009	−0.07	−0.29 to 0.42	0.71
	Functional activities	0.36	0.37	0.06 to 0.68	<0.05*
KOOS	Symptoms	0.09	0.03	−0.32 to 0.37	0.88
	Pain	0.07	0.05	−0.30 to 0.40	0.78
	ADL	0.28	0.42	0.11 to 0.73	<0.01*
	Sports/Recreation	0.12	0.12	−0.22 to 0.46	0.49
	QOL	0.16	0.21	−0.13 to 0.54	0.22
OKS		0.27	0.42	0.11 to 0.73	<0.01*

*$p < 0.05$.
KSS, Knee Society Score; KOOS, Knee injury Osteoarthritis Outcome Score; OKS, Oxford Knee Score.

These correlations indicate that higher muscle mass was associated with better functional activity, improved performance in daily activities, and enhanced knee function. PROs have been reported to accurately reflect the clinical status of patients, and to reveal various health problems they may face [15]. The results of this study thus indicate that OA patients with reduced skeletal muscle will face difficulties in ADL. Overall, our findings highlight the importance of muscle mass in patients with knee OA.

Regarding muscle mass in knee OA, numerous studies have investigated the relation between the strength of the quadriceps and the development or severity of knee OA. It is common for quadriceps strength to decrease in patients with knee OA [16]. Regarding the causes of this decline in quadriceps strength, a past report suggested that knee OA patients have higher rates of quadriceps cross-sectional area

reduction and intramuscular adipose tissue increase compared to non-OA patients, and both these phenomena are related to the decline in quadriceps strength and correlated with Western Ontario and McMaster Universities Arthritis Index (WOMAC) worthiness [17]. On the other hand, another report suggested that a reduction in quadriceps strength is only associated with pain, not with muscle atrophy [18], while other reports suggested that factors such as decreased muscle efficiency [19] or muscle dysfunction [16] also play a role in quadriceps strength. In short, the etiology of decline in quadriceps strength in OA remains controversial. However, these reports may be observing disease-specific changes caused by OA.

On the other hand, sarcopenia is an age-related change that affects the entire body and differs in its implications from disease-specific muscle changes. Sarcopenia is not uncommon in patients with end-stage knee OA [20]. Several studies have reported on the association between OA and sarcopenia. A previous report suggested that end-stage knee OA in patients with obesity and low muscle mass is associated with impaired physical function [21]. Another report revealed that obesity and sarcopenia were associated with knee OA [22]. A longitudinal, 60-month follow-up study reported that obesity and sarcopenic obesity — but not sarcopenia — were associated with the risk of knee OA [23]. These studies include the potent impact of obesity on knee OA. Another report revealed that sarcopenia was related to age-related knee OA [24]. On the other hand, there is a report that low skeletal muscle mass in the lower limb, not in the whole body, was associated with knee OA [25]. Finally, whole-body skeletal muscle mass has been found to correlate with knee OA in men, while fat mass correlated with knee OA in women [26]. To resolve the relation among skeletal muscle mass, fat mass and knee OA, future investigations will be needed, with consideration for differences in the target population or gender.

It is worth noting that the above-described studies primarily focused on examining the association between sarcopenia and radiographic OA. They did not specifically address how sarcopenia impacts the daily lives of individuals suffering from OA. To the best of our knowledge, the present investigation is the first to examine the impact of skeletal muscle loss on the lives of patients with advanced OA using SI and PROs, and to show that skeletal muscle loss is associated with lower ADL and functional activity scores.

TKA is the primary treatment for advanced knee OA; however, sarcopenia can sometimes impact TKA outcomes. It has been reported that TKA can improve clinical scores, gait speed, and muscle strength even in patients with sarcopenia. Interestingly, a previous study reported that 26% of a cohort of sarcopenic patients transitioned to a non-sarcopenic state after undergoing TKA [20]. On the other hand, other previous reports indicated that patients with sarcopenia experience a higher frequency of postoperative complications such as infection, falls, and fractures following TKA [27,28]. Therefore, managing these patients requires special attention. Regarding risk management, a previous study has discussed perioperative screening methods for sarcopenia that do not directly measure skeletal muscle mass. Instead, they utilize formulas based on muscle strength, physical performance, and nutritional status [29]. However, it is important to note that these assessments may not provide accurate results for patients suffering from painful OA. In this regard, the present study contributes significantly by introducing a simple method for estimating skeletal muscle mass using SI. While precise measurements typically require DXA or BIA, the utilization of SI allows for the estimation of skeletal muscle mass from basic blood samples, eliminating the need for advanced facilities. In addition, the diagnosis of sarcopenia in patients with advanced knee OA may be influenced by pain-related disabilities and impaired physical function. Therefore, the application of SI to the estimation of skeletal muscle mass from blood samples may serve as a useful tool in evaluating sarcopenia in patients with OA and other painful musculoskeletal disorders. Furthermore, SI is simpler than physical function assessment and is suitable for longitudinal and repeated evaluations, potentially allowing for a straightforward estimation of postoperative skeletal muscle changes in OA patients.

Limitations. Despite the valuable insights gained from our study, several limitations should be acknowledged. First, the retrospective design and relatively small sample size might limit the generalizability of our findings. Future prospective studies with larger cohorts are warranted to validate our results and further elucidate the relationship between skeletal muscle mass and functional outcomes in advanced knee OA. Secondly, our study focused on estimating skeletal muscle mass using SI as a surrogate marker. While SI has shown

promising associations with muscle mass and physical function, it should be noted that SI is not included in the current diagnostic criteria for sarcopenia. Future studies should aim to establish validated cut-off values for SI with physical function assessment including grip strength and calf circumference, and investigate its utility in diagnosing sarcopenia and predicting functional outcomes in patients with advanced knee OA. Moreover, our study primarily focused on functional outcomes and did not extensively explore the underlying mechanisms linking skeletal muscle mass to functional impairments in advanced knee OA. Further research is needed to investigate the intricate interactions among muscle mass, joint biomechanics, pain perception, and other contributing factors to gain a comprehensive understanding of the underlying mechanisms and develop targeted interventions.

In conclusion, reduced skeletal muscle mass as assessed by SI affects ADL and functional activity in patients with advanced knee OA. Because the use of SI to estimate skeletal muscle mass is relatively simple, SI may prove helpful in determining the preoperative status of patients and assessing the operative risk.

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