



# Influence of the severity of knee osteoarthritis on the association between leg muscle mass and quadriceps strength: the SPSS-OK study

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## Abstract

Quadriceps strength is important for maintaining functional movement in patients with knee osteoarthritis (OA). We aimed to examine whether knee OA severity weakened the magnitude of the associations between leg muscle mass, quadriceps strength, and functional movement. Screening for People Suffering Sarcopenia in Orthopedic cohort of Kobe study (SPSS-OK) was a single-center cross-sectional study. We recruited 611 patients with knee OA. Leg muscle mass was determined by bioimpedance and used as a proxy for quadriceps muscle mass. Quadriceps strength and indices of functional movement (assessed by the functional activities category of the new Knee Society Score questionnaire [KSS] and the Timed Up and Go [TUG] test) were measured. Knee OA severity was determined by the Kellgren-Lawrence radiographic grade. A series of general linear models was fitted with adjustment for confounding variables. The increase in quadriceps strength per leg associated with a 1-kg increase in leg mass per leg was 7.29 Nm, 5.43 Nm, and 3.77 Nm among patients with knee OA grade 1/2, 3, and 4, respectively ( $P$  for interaction = 0.003). A 1-Nm increase in quadriceps strength per leg was associated with both a 0.14 point increase in KSS movement score and a 0.05 s decrease in TUG, regardless of knee OA severity ( $P$  for interaction 0.430 and 0.323). Severe knee OA may reduce efficiency in the exertion of quadriceps strength by leg muscle mass even when the amount of muscle mass remains unchanged.

**Keywords** Knee osteoarthritis severity · Muscle mass · Muscle strength

## Introduction

Osteoarthritis (OA) of the knee is a common musculoskeletal disorder and a leading cause of pain and disability in the elderly.

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The prevalence of knee OA based on radiographic evidence was 37% in adults aged 60 years or older in the USA [1] and 47 to 70% in adults aged 40 years or older in Japan [2]. In addition, the care associated with the functional disability of knee OA has a substantial economic impact on society, as was reported from the UK [3]. Thus, maintaining functional movement is an important aspect of care for this condition, as avoiding knee surgery may reduce its economic burden.

Quadriceps strength can be the major determinant of functional movement of the knee and is a potential target for rehabilitation in patients with knee OA [4]. However, the relationships between lower limb muscle mass, quadriceps strength, and functional movement are not clearly understood. Contrary to the general principle that muscle strength is determined by muscle mass [5], one study in knee OA patients found no association between increasing quadriceps strength and increasing quadriceps muscle mass [6], while a second suggested that quadriceps weakness may be present even when quadriceps muscle atrophy is not [7]. With regard to the connection between the quadriceps and the severity of knee OA, a decrease in quadriceps strength associated with an increase in knee OA severity has been reported [8, 9]. These findings indicate that the relationship between quadriceps muscle mass

and quadriceps strength can be affected by the structural severity of knee OA; in other words, compared to patients with less severe knee OA, the magnitude of the association between quadriceps muscle mass and quadriceps strength among those with more severe knee OA may decrease, even when the amount of muscle mass remains the same. To date, however, no study has yet examined the relationship between leg muscle mass and quadriceps strength with consideration to the structural severity of knee OA. Moreover, few studies have examined whether structural severity affects the association between quadriceps strength and functional movement. Clarification of these mechanisms is clinically important because it will allow clinicians to consider knee OA severity in efforts to increase quadriceps strength and improve functional movement.

Here, we investigated whether the structural severity of knee OA modifies the relationships between quadriceps muscle mass, quadriceps muscle strength, and functional movement, using data from the large, single-center, cross-sectional “Screening for People Suffering Sarcopenia in Osteoarthritis cohort of Kobe” (SPSS-OK) study.

## Methods

### Design, setting, and participants

Patients were recruited consecutively from August 2016 to February 2018. The study center is located in the central part of Kobe, Japan. Our target population was patients with knee OA who were scheduled for knee replacement surgery, and included only those patients awaiting first replacement surgery to avoid the potential interference of an implanted artificial joint on bioimpedance analysis (BIA). The study was approved by the local institutional review board and by the Research Ethics Committee of Fukushima Medical University School of Medicine. Because this study was an observational study using anonymized medical information collected during routine practice, informed consent was not mandatory according to Japanese ethical guidelines for medical and health research involving human subjects.

### Conceptual framework

A conceptual framework is shown in Supplementary Fig. 1. First, we focused on the relationship between leg muscle mass as exposure and quadriceps strength as outcome, with knee OA severity as effect modifier (analysis #1). Next, we focused on the relationship between quadriceps strength as exposure and indices of functional movement as outcomes, with knee OA severity as effect modifier. The indices used in this study were patient-reported movement score determined by the KSS

movement score (analysis #2) and objective score determined by the Timed Up and Go test (analysis #3).

### Knee OA severity

Radiographs were evaluated and graded by a single trained observer (OW) based on the Kellgren-Lawrence radiographic grading system [10]. Intra-rater reliability for radiographic severity was assessed by reassessment of 100 randomly selected radiographs 2 weeks later and found to be excellent ( $\kappa = 0.89$ ).

### Single leg muscle mass as a proxy for single quadriceps muscle mass

Single leg muscle mass was assessed as a proxy for quadriceps muscle mass and measured by BIA using a MC-780A (Tanita, Tokyo, Japan) during a pre-surgical evaluation conducted while the patient was in a stable condition. Quadriceps muscle volume accounts for approximately one-quarter of total single leg muscle volume, with the vastus lateralis, vastus medialis, vastus intermedius, and rectus femoris at approximately 12%, 6%, 4%, and 4%, respectively [11]. The monitor is a multifrequency device which measures bioimpedance at 3 frequencies between 5 and 250 kHz. The results were analyzed by an on-board body composition analyzer. Validation of the BIA method using a DXA method (DPX-L, GE Healthcare) showed very high correlations between the two methods for both fat mass (unit kg,  $DXA = BIA \times 1.0066 + 0.0305$ ,  $r = 0.9595$ , standard error of the estimate [SEE] = 1.718) and appendicular skeletal muscle mass (unit kg, lean soft tissue mass by DXA = skeletal muscle mass by BIA  $\times 1.0065 - 0.0722$ ,  $R = 0.9889$ , SEE = 1.704).

### Quadriceps strength

Quadriceps strength was measured as peak isometric knee extension torque (Nm) using a handheld dynamometer ( $\mu$ Tas F1; Anima, Chofu, Japan). This method uses a belt to measure the strength of knee extension, and has been shown to be highly reliable [12] and to produce results consistent with those of the isokinetic dynamometer method [13]. Participants were seated with their hips flexed to 90° and the knees flexed to 75°. They were instructed to extend a knee maximally for 3 s under verbal encouragement to facilitate maximal volitional force production. Peak torque was estimated as the product of the force being exerted and the distance between the attachment of the dynamometer and the center of rotation of the knee joint. Maximal contraction was attempted twice, and the trial that produced the higher volitional force was normalized to body weight and used for analysis.

### Functional movement: functional movement score and timed up and go

Functional movement was assessed using two measures: the new Knee Society Score questionnaire (new KSS) [14] and the Timed Up and Go (TUG) test [15]. The new KSS is a self-reported and validated questionnaire [16] which reflects physical activity in Japanese populations [17]. We chose the functional activities category of the new KSS to measure the degree of functional movement (19 items, 100 points). This category is divided into walking and standing (5 items, 30 points), standard activities (6 items, 30 points), advanced activities (5 items, 25 points) and discretionary activities (3 items, 15 points), with higher scores representing better physical functioning. The TUG test measures the time it takes the participant to rise from a no-arm chair (seat height, 40 cm), walk 3 m, turn, and return to sitting in the same chair. Participants were instructed to walk as quickly as possible so long as they felt safe and comfortable. Assistive devices were allowed only if the participant felt unsafe or could not complete the test without the assistance. The average of two consecutive trials was used for analysis.

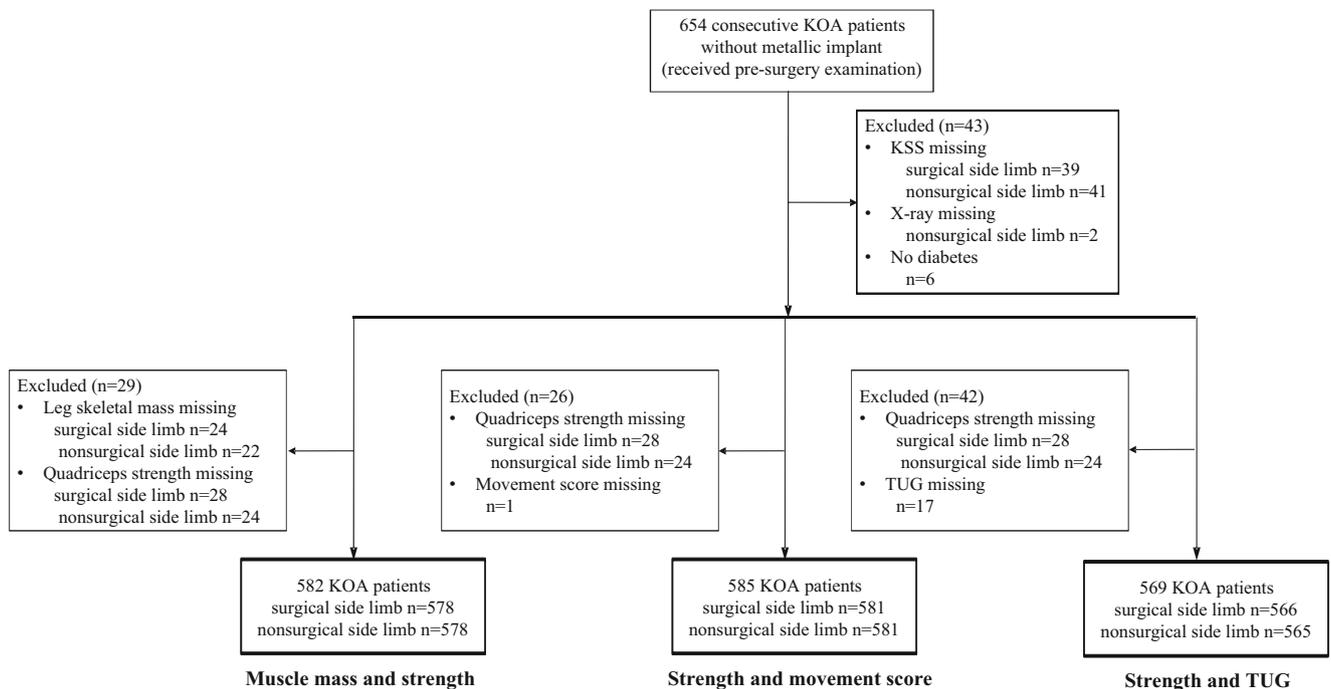
### Measurement of covariates

Potential confounding variables examined were sociodemographic characteristics including age, gender, fat mass as measured by BIA, presence of type 2 diabetes, and knee pain. The presence of type 2 diabetes was defined as a

glycosylated hemoglobin (HbA1c) level  $\geq 6.5\%$  [18] and the degree of knee pain per leg was measured by the 1-item KSS pain score on walking on level ground, ranging from 0 = no pain to 10 = worst pain [16].

### Statistical analysis

All statistical analyses were conducted using Stata/SE version 15 (Stata Corp., College Station, TX). Complete case analyses were done because the proportion of patients with missing data was small. Baseline characteristics were described using appropriate summary statistics. For analysis #1, we fitted a general linear model to estimate mean differences in quadriceps strength by differences in leg muscle mass, with adjustment for age, sex, diabetes, fat mass, KSS pain score, and side for planned surgery, and considering clustering effects by individuals using cluster-robust variance to justify per limb analysis. To estimate the modification of associations between leg muscle mass and quadriceps strength by knee OA severity, knee OA severity categories (grade 1/2, 3, or 4) were entered into the general linear model with interaction terms with the leg muscle mass variable. Interactions were assessed using the Wald test. For analyses #2–#3, we separately fitted general linear models to estimate mean differences in indices of functional movement (i.e., KSS movement score for #2 and Timed Up and Go for #3) by differences in quadriceps strength, with adjustment for age, sex, diabetes, fat mass, KSS pain score, and side of planned surgery, and considering clustering effects by individuals using cluster-robust variance to justify per limb



**Fig. 1 Patient flow.** Exclusion of patients who lacked exposure and outcome variables for analyses #1–#3 and 582, 585, and 569 patients were included from analyses #1–#3, respectively

analysis. To estimate the modification of associations between quadriceps strength and indices of functional movement by knee OA severity, knee OA severity categories (grade 1/2, 3, or 4) were entered into the general linear model with interaction terms with the quadriceps strength variable. A  $P$  value < 0.05 was considered to indicate statistical significance.

## Results

### Patient flow and descriptive statistics

Initially, 654 patients with knee OA who met the inclusion criteria were identified. Of these, 43 patients without the new KSS score, knee OA severity categories, or diabetes were excluded. After further exclusion of patients who lacked exposure and outcome variables for analyses #1–#3, 582, 585, and 569 patients were included from analyses #1–#3, respectively (Fig. 1). Table 1 summarizes the baseline characteristics of the study population. Mean age (standard deviation) was 72.5 (7.8) years, and over three-quarters (78%) were female.

### Effect modification on the association between leg muscle mass and quadriceps strength by knee OA severity

Table 2 shows the association between leg muscle mass and quadriceps strength by the severity of knee OA. The association between leg muscle mass and quadriceps strength per limb differed by knee OA severity, with the association weakening with increasing severity ( $P$  for interaction = 0.003). For example, a 1-kg increase in leg muscle mass was associated with a 7.29-Nm (95% confidence interval 5.10–9.48) increase in quadriceps strength in patients with grade 1 or 2 OA, versus only a 3.77-Nm (95% CI 1.62–5.93) increase in patients with grade 4 disease.

### Effect modification on the association between quadriceps strength and functional movement by knee OA severity

Tables 3 and 4 show the associations between quadriceps strength and indices of functional movement. Knee OA severity was not shown to modify the associations between quadriceps strength per leg and KSS movement score or TUG test time ( $P$  for interaction: 0.430 and 0.323, respectively), with stronger quadriceps muscle strength associated with both a higher movement score in the new KSS (0.14 points per 1 Nm increase, 95%CI: 0.08 to 0.19) and a shorter TUG test time (−0.05 s per 1 Nm increase, 95% CI −0.06 to −0.03).

**Table 1** Baseline characteristics of knee OA patients

	Total	
	N = 611	
Age, years	72.5	(7.8)
Female, $n$ (%)	474	(78%)
Fat mass, kg	20.0	(7.9)
Diabetes, $n$ (%)	60	(10%)
X-ray grade, $n$ (%)		
Surgical side		
Grade 1	0	(0%)
Grade 2	32	(5%)
Grade 3	122	(20%)
Grade 4	457	(75%)
Nonsurgical side		
Grade 1	8	(1%)
Grade 2	172	(28%)
Grade 3	161	(26%)
Grade 4	268	(44%)
Missing $n = 2$		
Leg skeletal mass, kg		
Surgical side	6.6	(1.7)
Missing $n = 24$		
Nonsurgical side	6.7	(1.7)
Missing $n = 24$		
Quadriceps strength, Nm		
Surgical side	47.8	[35.3; 63.5]
Missing $n = 28$		
Nonsurgical side	58.4	[45.3; 73.8]
Missing $n = 27$		
KSS movement score, points	47.4	(17.0)
Missing $n = 1$		
KSS pain score on walking on level ground, points		
Surgical side	5	[3; 8]
Missing $n = 1$		
Nonsurgical side	2	[0; 5]
Missing $n = 3$		
Timed Up and Go, sec	10.6	(3.7)
Missing $n = 17$		

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

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

The 611 patients all had complete data on KSS pain score and knee X-rays for either the surgical side or nonsurgical side, and had data on diabetes. These 611 patients remained after the exclusion of 43 patients from 654 patients, as presented in Fig. 1. Notwithstanding the inclusion criteria, KSS pain score might still have been missing in cases in which the KSS pain score was unavailable for one side but available for the other side

**Table 2** Association between leg muscle mass and leg strength by knee osteoarthritis grade

Quadriceps strength per limb, Nm	Osteoarthritis grade	Adjusted mean difference	95% confidence interval		P value
			Lower	Upper	
Leg muscle mass per limb, kg <sup>a</sup>	1 or 2	7.29	5.10	9.48	< 0.001
	3	5.43	2.84	8.02	< 0.001
	4	3.77	1.62	5.93	0.001
Age, year		- 0.60	- 0.81	- 0.38	< 0.001
Sex, female		- 17.32	- 24.95	- 9.70	< 0.001
Diabetes, yes		1.75	- 4.01	7.51	0.552
Total fat mass, kg		- 0.05	- 0.28	0.17	0.642
KSS pain score per limb, point		- 1.65	- 2.10	- 1.19	< 0.001

Analysis of 1156 limbs among 582 knee osteoarthritis patients

General linear model adjusted for age, gender, diabetes, fat mass, side of planned surgery, pain score, and X-ray grade with consideration to intra-individual correlation using cluster-variance

Italic font indicates significance at *P* < 0.05 in *P* value column and corresponding point estimate and 95% confidence interval in adjusted mean difference columns

<sup>a</sup> Within each osteoarthritis grade subcategory, the adjusted mean differences are estimated because osteoarthritis grade modified the association between leg muscle mass and quadriceps strength (*P* for interaction = 0.003)

### Discussion

In this large cross-sectional study, we found that the strength of association between leg muscle mass and quadriceps strength per limb decreased with increasing severity of knee OA. In contrast, quadriceps strength per limb was associated with indices of functional movement regardless of knee OA severity. Our findings suggest that training to increase quadriceps muscle mass may be less efficient in increasing quadriceps strength with increasing severity of knee OA. This may in turn warrant provision of individualized rehabilitation programs according to knee OA severity.

Our findings for the mechanism by which knee OA severity modifies the relationship between leg muscle mass and

quadriceps strength can be explained by previous studies. First, the decrease in quadriceps strength in patients with severe disease was partly due to the presence of arthrogenous muscle inhibition (AMI), which is attributable to altered afferent input from the damaged joint and a consequent reduction in efferent motor neuron output to the quadriceps [19]. We speculate that this change in afferent input is greater with more severe joint damage, and thus the severely damaged knee may hinder the exertion of strength despite the same muscle mass. Second, inadequate exertion of knee extension in patients with severe knee OA may result from coexisting patellofemoral OA. Worsening of patellofemoral OA has been associated with more severe varus knee deformity [20], and the presence of more severe coexisting patellofemoral OA is associated

**Table 3** Association between quadriceps strength and KSS movement score

KSS movement score, points	Adjusted mean difference	95% confidence interval		P value
		Lower	Upper	
Quadriceps strength per limb, Nm <sup>a</sup>	0.14	0.08	0.19	< 0.001
Age, year	- 0.47	- 0.64	- 0.30	< 0.001
Sex, female	2.95	- 0.48	6.38	0.092
Diabetes, yes	- 1.65	- 5.57	2.27	0.409
Total fat mass, kg	- 0.39	- 0.55	- 0.22	< 0.001
KSS pain score per limb, point	- 1.74	- 2.17	- 1.31	< 0.001

Analysis of 1162 limbs among 585 knee osteoarthritis patients

General linear model adjusted for age, gender, diabetes, fat mass, side of planned surgery, pain score, and X-ray grade with consideration for intra-individual correlation using cluster-variance

Italic font indicates significance at *P* < 0.05 in *P* value column and corresponding point estimate and 95% confidence interval in adjusted mean difference columns

<sup>a</sup> The adjusted mean difference did not differ by knee osteoarthritis grade because osteoarthritis grade was not shown to modify the association between quadriceps strength and KSS movement score (*P* for interaction = 0.430)

**Table 4** Association between quadriceps strength and Timed Up and Go score

Timed Up and Go, sec	Adjusted mean difference	95% confidence interval		<i>P</i> value
		Lower	Upper	
Quadriceps strength per limb, Nm <sup>a</sup>	<i>- 0.05</i>	<i>- 0.06</i>	<i>- 0.03</i>	<i>&lt; 0.001</i>
Age, year	<i>0.17</i>	<i>0.13</i>	<i>0.20</i>	<i>&lt; 0.001</i>
Sex, female	<i>- 0.87</i>	<i>- 1.60</i>	<i>- 0.13</i>	<i>0.022</i>
Diabetes, yes	0.08	- 0.84	1.01	0.859
Total fat mass, kg	<i>0.11</i>	<i>0.07</i>	<i>0.16</i>	<i>&lt; 0.001</i>
KSS pain score per limb, point	<i>0.23</i>	<i>0.13</i>	<i>0.33</i>	<i>&lt; 0.001</i>

Analysis of 1131 limbs among 569 knee osteoarthritis patients

General linear model adjusted for age, gender, diabetes, fat mass, side of planned surgery, pain score, and X-ray grade with consideration for intra-individual correlation using cluster-variance

Italic font indicates significance at  $P < 0.05$  in  $P$  value column and corresponding point estimate and 95% confidence interval in adjusted mean difference columns

<sup>a</sup> The adjusted mean difference did not differ by knee osteoarthritis grade because osteoarthritis grade was not shown to modify the association between quadriceps strength and Timed Up and Go ( $P$  for interaction = 0.323)

with significantly lower knee extension strength [21]. Third, our finding might indirectly corroborate a previous pathological evaluation of quadriceps muscle quality which found that patients with knee OA had a decrease in type I fiber and stellate cell density and an increase in extracellular matrix with reduced quadriceps strength compared with normal control, despite similar muscle volume [22]. Fourth, torque production in knee extension is compromised by the change in the quadriceps lever arm associated with knee OA deformity. This is because the dispersion of knee extension force into knee abduction or adduction torque under severe knee deformity prevents the maximization of knee extension torque.

The associations between quadriceps strength and indices of functional movement regardless of the severity of knee OA are consistent with previous studies. Barker et al. [23] reported that lower extremity power was strongly correlated with functional performance, while Chun et al. [4] demonstrated that quadriceps strength is the main determinant of physical performance in patients with knee OA regardless of knee OA severity.

Our findings have two implications for clinicians. First, strategies aimed at improving functional movement should be customized in accordance with the severity of knee OA. Patients with less severe knee OA can be provided a more efficient approach to increasing quadriceps muscle mass than those with severe disease, leading to greater quadriceps strength and functional movement. For patients with severe disease, in contrast, the correlates of indices of functional movement suggest that factors other than quadriceps strength should also be incorporated into the training program, such as a reduction in total fat mass and alleviation of knee pain [24], on the basis that a focus on quadriceps training may be less effective than in less severe disease. Second, to improve the functional movement of patients with knee OA, quadriceps muscle strengthening should be emphasized as a targeted treatment program.

Our study has several strengths. First, its large-scale, single-center design allowed us to measure muscle mass, strength and mobility (i.e., Timed Up and Go test) in a uniform way. Second, we attempted to analyze both lower limbs in each patient using a suitable statistical method. Accordingly, our findings can be applied to both lower limbs in a single patient with knee OA, given that OA often affects both knees, and the design of an effective rehabilitation program can therefore take both lower limbs into consideration.

Several limitations should also be noted. First, the cross-sectional design does not allow the assigning of causality. Second, leg muscle mass determined by BIA includes not only the quadriceps muscle mass but also that of portions of other leg muscles. Although determining the anatomical cross-sectional area of the quadriceps muscles would aid in determining the exact quadriceps muscle mass, this was not possible in this study because of the cost and radiation risk of computed tomography and the cost and time burden of magnetic resonance imaging. Nevertheless, given that the quadriceps femoris is the largest of all muscles of the lower extremity [11], we believe that leg muscle mass determined by BIA is a reasonable proxy for quadriceps muscle mass. Third, the participants in this study were not representative of total knee OA patients, as most of the participants had severe radiographic knee OA awaiting knee replacement surgery. However, we believe that dependence of the association between leg muscle mass and quadriceps strength on the severity of knee OA is a valuable finding that should be validated using different source population such as patients who don't require surgical treatment.

In conclusion, our study showed that the magnitude of the association between leg muscle mass and quadriceps strength is weakened with severer knee OA. In contrast, the association between quadriceps strength and functional performance is consistent regardless of severity. Further longitudinal studies

are required to determine whether training for increased quadriceps muscle mass in patients with more severe OA of the knee results in a smaller increase in quadriceps strength.

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## Compliance with ethical standards

**Disclosures** None.

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