A commentary by Gregory J. Golladay, MD, is linked to the online version of this article.

Perioperative Essential Amino Acid Supplementation Facilitates Quadriceps Muscle Strength and Volume Recovery After TKA

A Double-Blinded Randomized Controlled Trial

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Background: Perioperative essential amino acid (EAA) supplementation suppresses lower-limb muscle atrophy and promotes functional improvement in the first 4 weeks after total knee arthroplasty (TKA). However, its effect on the recovery of muscle volume and strength in the intermediate term is unclear. The aim of this study was to evaluate the effect of perioperative EAA supplementation on the recovery of lower-limb muscle volume and strength in the 2 years after TKA.

Methods: Sixty patients who underwent unilateral TKA for primary knee osteoarthritis were included in this double-blinded randomized controlled trial. After excluding dropouts, 26 patients assigned to the EAA group (9 g/day) and 26 assigned to the placebo group (powdered lactose, 9 g/day) were available for analysis. Patients received EAA supplementation or a placebo from 1 week prior to surgery to 2 weeks after it. The rectus femoris muscle area was measured using ultrasonography and quadriceps muscle strength was measured isometrically with a handheld dynamometer, preoperatively and periodically up to 2 years postoperatively. Knee pain, knee range of motion, functional mobility, and Knee Society Score 2011 subjective scores were measured at each time point. Perioperative management, except for supplementation, was identical in the 2 groups.

Results: Taking the baseline as 100%, the mean values in the EAA and placebo groups were 134% ± 31% and 114% ± 27%, respectively, for the rectus femoris muscle area and 159% ± 54% and 125% ± 40% for the quadriceps muscle strength, respectively, at 2 years after surgery. The differences were significant ($p < 0.05$). Clinical outcomes were not significantly different between the 2 groups.

Conclusions: Perioperative EAA supplementation contributes to the recovery of rectus femoris muscle volume and quadriceps muscle strength in the 2 years after TKA. The EAA supplementation did not impact clinical outcomes.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Total knee arthroplasty (TKA) for degenerative arthritis of the knee has demonstrated good clinical results[1]. However, lower-extremity muscle volume and strength decrease after TKA, leading to complications such as falls and possible readmission[2,3].

Perioperative essential amino acid (EAA) supplementation in patients undergoing TKA has been shown to reduce rectus femoris muscle atrophy in the first 4 weeks after TKA[4]. Elderly individuals do not recover lost muscle strength in the lower extremity as readily as young individuals do[5]. Therefore, the effect of suppressing perioperative muscle atrophy might be prolonged into the intermediate term after TKA because the average age of patients who have undergone primary TKA has been described as elderly[6,7]. However, the effect of EAA supplementation in the intermediate term after surgery is unknown, to our knowledge.

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/H362).

A **data-sharing statement** is provided with the online version of the article (http://links.lww.com/JBJS/H364).

The aim of this study was to test the hypothesis that suppressing muscle atrophy with perioperative EAA supplementation will have a favorable effect on the recovery of lower-limb muscle volume and strength in the intermediate term (2 years) after TKA.

Materials and Methods

Study Design

This study was a 2-arm, parallel trial with 1:1 allocation to EAA and placebo groups. Concealed sequential numbers were used to randomize 30 patients to each group[8]. Only the medical staff, who were not involved in the study, opened the envelopes and handled the assigned information. Baseline measurements were obtained 1 month before surgery. Outcomes, with the exception of serum albumin level and radiographic assessment, were measured at baseline and at 1, 2, 3, and 4 weeks, 6 months, and 1 and 2 years postoperatively. Seventy-seven patients scheduled to undergo unilateral TKA for knee osteoarthritis were potentially eligible for the study. Exclusion criteria were (1) an etiology other than knee osteoarthritis, (2) severe hepatic or renal disease or other conditions that could affect the metabolism of nutrients, and (3) scheduled TKA of the contralateral knee. After application of the exclusion criteria, 60 patients were enrolled. Four patients in each group were lost to follow-up; therefore, 52 patients were available for the analysis (Fig. 1). Prior to participant recruitment, the study protocol was registered in the UMIN Clinical Trials Registry (000034997) and approved by the institutional review board (approval no. 00012018). All patient provided written informed consent prior to their involvement in the trial.

Perioperative Management

A single surgeon performed all TKAs using the same operative method and implant (EVOLUTION; MicroPort). Briefly, a medial parapatellar approach and a measured resection technique were used. All patients were hospitalized from a few days prior to TKA until 4 weeks after TKA; during hospitalization, the same nutritional and physical therapies were provided, with the exception of the EAA supplementation. The length of hospitalization was standardized to 4 weeks after TKA for all

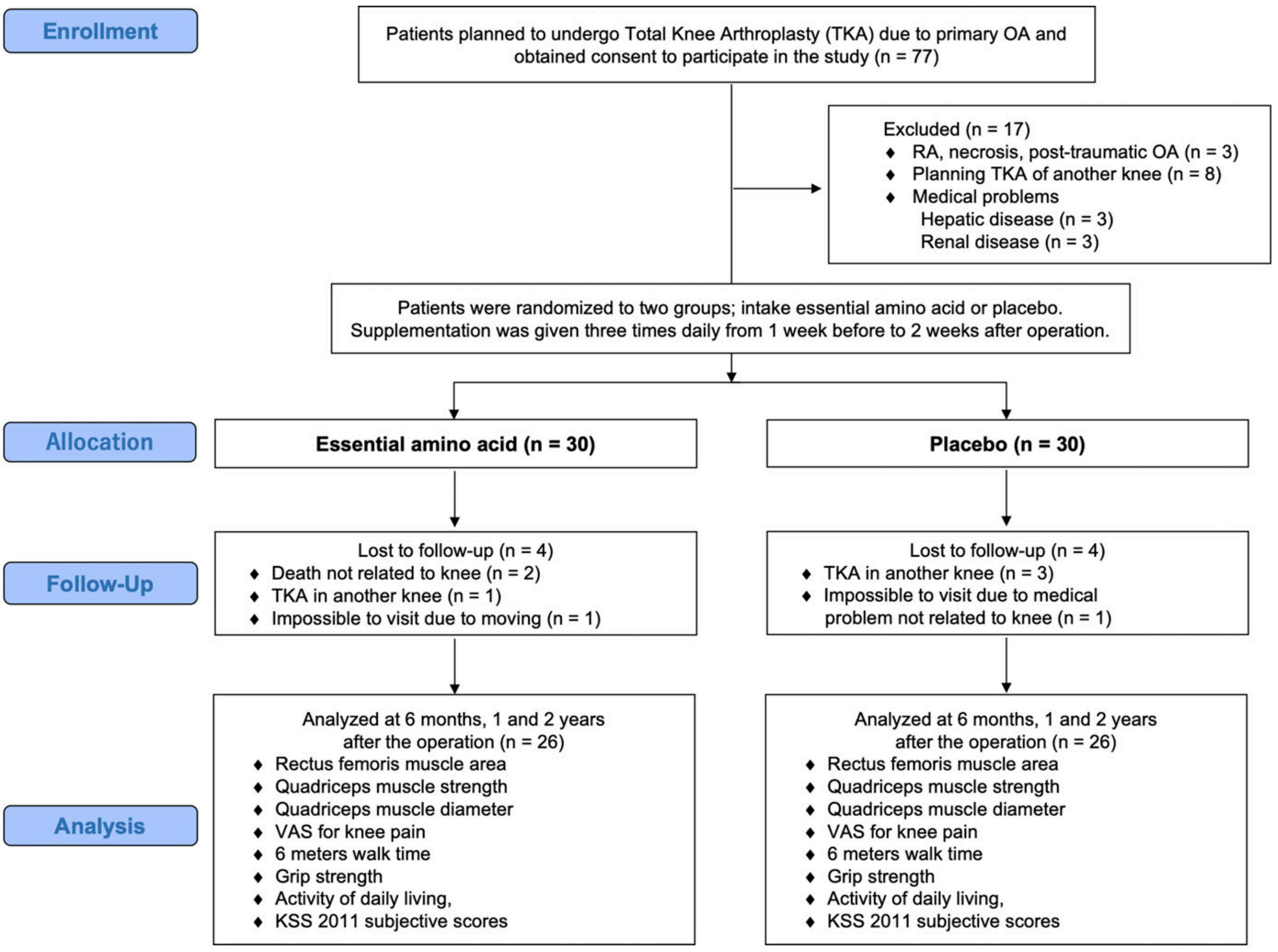

Fig. 1

CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study. OA = osteoarthritis, RA = rheumatoid arthritis, VAS = visual analogue scale, KSS = Knee Society Score.

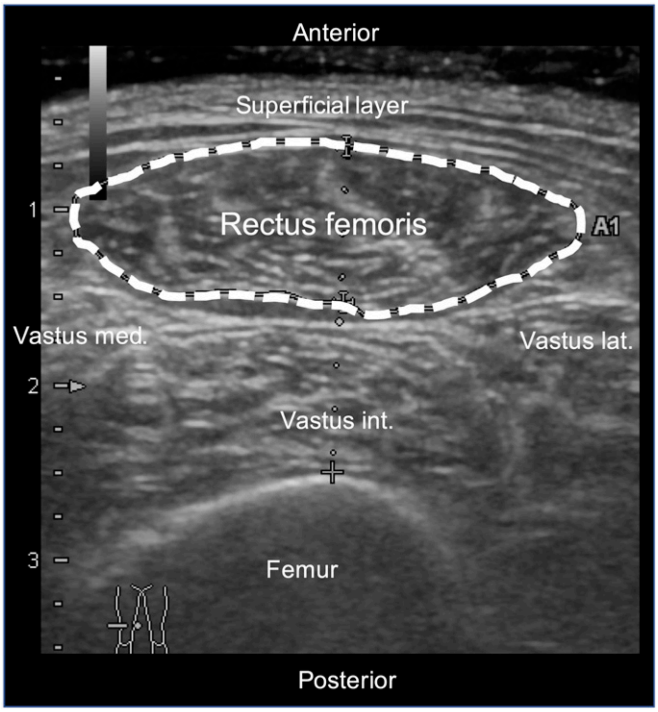

Fig. 2
Ultrasonographic measurements of the rectus femoris muscle area. The white circle shows the axial rectus femoris muscle area measured on a static image. The measurement location was two-thirds of the distance between the anterior superior iliac spine and the superior border of the patella.

patients to ensure strict perioperative nutritional management. Patients were informed of and consented to this hospitalization prior to study enrollment.

Nutritional Intervention

From 1 week prior to TKA until 2 weeks after it, patients received 3 g of EAA or a placebo (lactose powder) 3 times daily (after every meal). The total amount of supplementation was 9 g/day. The daily dosage of EAA contained the following amino acids: threonine (405 mg, 4.5%), lysine (756 mg, 8.4%), isoleucine (603 mg, 6.7%), valine (603 mg, 6.7%), methionine (603 mg, 6.7%), tryptophan (207 mg, 2.3%), phenylalanine (405 mg, 4.5%), leucine (684 mg, 7.6%), histidine (315 mg, 3.5%), arginine (630 mg, 7%), and glycine (1,089 mg, 12.1%); the remainder was starch (2,700mg, 30%). The Japanese government has approved the commercial packaging of this amount of EAA supplement (ES-Polytamin; EA Pharma) for the purpose of preventing perioperative undernutrition.

Outcomes

The primary outcome was the rectus femoris muscle area as assessed by ultrasonography. The secondary outcomes were quadriceps muscle strength, diameter of the quadriceps muscle, knee pain on a visual analogue scale (VAS), 6-meter walk time, grip strength, knee range of motion, functional mobility, Knee Society Score 2011 (KSS 2011) subjective scores, and radiographic femorotibial and prosthesis alignment angles. Serum albumin level and food preferences were also measured.

The rectus femoris muscle area was measured as described previously[4]. During examination, the knee was extended with the patient relaxed in the supine position. An 8-mHz linear probe with a 5.6-cm array (Xario ssA-660A; Toshiba Medical Systems) was positioned, with minimal pressure, perpendicular to the long axis of the femur. The measurement point was two-thirds of the distance between the anterior superior iliac spine and the superior border of the patella. One technician, who was blinded to the group assignment, measured the rectus femoris muscle area and diameter based on the outline of the muscle (Fig. 2). The intraclass correlation coefficient (ICC) for this measurement was evaluated by making 2 measurements separated by a 4-week interval. The ICC was interpreted as follows: 0 to 0.40, poor; 0.41 to 0.60, moderate; 0.61 to 0.80, good; and 0.81 to 1.00, excellent[9]. The ICC was 0.85 (95% confidence interval [CI], 0.48 to 0.97).

The quadriceps muscle strength was measured using a digital pull-type handheld dynamometer (Mobie; Sakaiika).

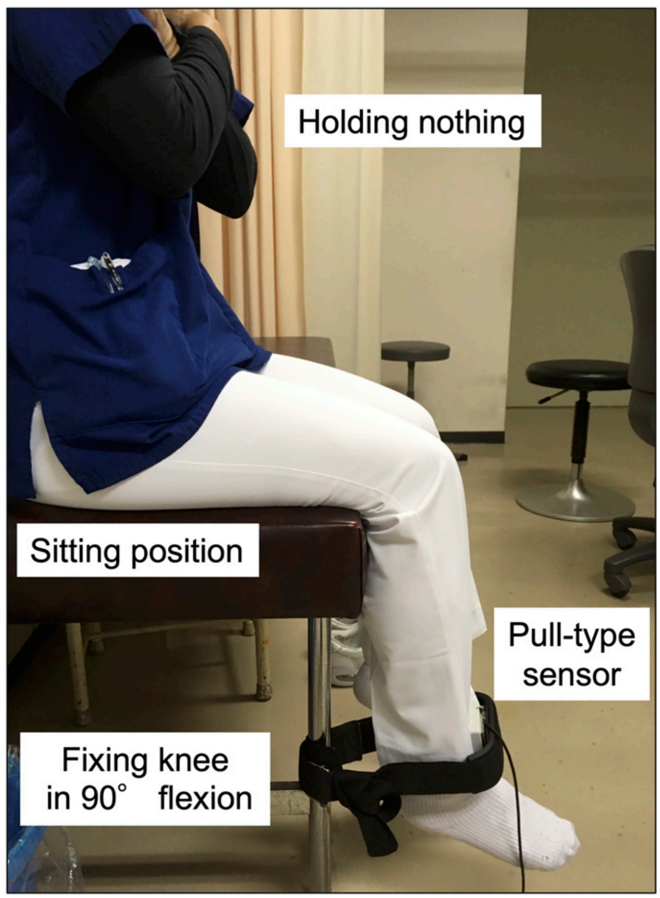

Fig. 3
Measurements of quadriceps muscle strength. Patients sat with 90° of knee flexion, with their hands and feet not in contact with anything. Isometric quadriceps muscle strength was measured with a pull-type handheld dynamometer.

Patients sat on the edge of the bed, holding nothing in their hands, with their feet off the ground, and the dynamometer band was fastened to the ankle for quantification (Fig. 3). They were instructed to extend the knee as much as possible, and the isometric quadriceps muscle strength was recorded[10]. The validity of the strength measurements was assessed in advance; 2 physical therapists each performed 2 quadriceps muscle strength measurements separated by a 2-week interval, and the ICC was calculated. The intraobserver ICC was 0.88 (95% CI, 0.73 to 0.95) and the interobserver ICC was 0.78 (95% CI, 0.51 to 0.91). The quadriceps diameter was measured as the distance from the superficial layer to the femur on the same sonogram on which the rectus femoris muscle area was measured. A nurse recorded the patient's knee pain reported on a VAS with a scale of zero (no pain) to 10 (worst possible pain). The 6-meter walk time was calculated as the time required to walk 6 m at the patient's "comfortable speed."[11] Knee range of motion was measured using a goniometer[12]. Functional mobility was categorized according to walking ability as either "independent walk," "cane," "walker," or "wheelchair."[4] The serum albumin level was measured in a blood sample at baseline. Patients completed a questionnaire regarding their food preferences and were categorized as "meat-eaters," "fish-eaters," or "vegetarian" at each visit[13]. Radiographic assessments were performed at baseline and at the final 2-year follow-up to determine the femorotibial angle at each time point and the prosthesis alignment angles (α, β, δ, γ) at 2 years[14]. These were measured on standing short-film radiographs of the knee. Functional mobility outcomes were collected by physical therapists who were unaware of the group assignment, and the femorotibial angle was measured by an orthopaedic surgeon who was not involved in the surgical procedures.

Statistical Analysis

Continuous variables were described using the mean and standard deviation. Categorical variables were tabulated using absolute frequencies. The Student t test and the chi-square test were used in univariate analyses to assess the differences in continuous and categorical variables, respectively, between the 2 groups. A 2-way repeated analysis of variance with a post-hoc Bonferroni test was used to compare the chronological changes in continuous variables (i.e., relative changes in outcomes) between the 2 groups. Multivariate linear regression analysis was performed to identify predictors of the final recovery, with the relative change in rectus femoris muscle area at 2 years after TKA as the objective variable. Significance was set at $p < 0.05$. Based on preliminary data and a previous study with a similar cohort[2], a power analysis was conducted for an expected difference in the primary outcome measure of 15%. It was determined that a sample size of 24 patients in each group, with an assumed 2-tailed type-1 error rate of 0.05 and 80% power, would be enough to detect this difference between the 2 groups. Therefore, given an expected dropout rate of 10%[15,16], approximately 26 patients in each group were considered to be sufficient for this study. Statistical analyses were performed with R (version 3.1.1; R Foundation for Statistical Computing).

Source of Funding

No external funding was received for this study.

Results

Sixty patients were enrolled in the study, and 4 patients in each group were lost to follow-up. In the EAA group, 2 patients died due to reasons unrelated to the knee, 1 patient underwent TKA of the contralateral knee, and 1 patient moved and could not continue to visit the hospital. In the placebo group, 3 patients underwent TKA of the contralateral knee and 1 patient could not continue to visit the hospital due to medical problems unrelated to the knee. The remaining 26 patients in each group were analyzed. Patient demographics are shown in Table I. Serum albumin levels and food preferences did not differ significantly between the groups at baseline. There were no vegetarians in the study. Food preferences were unchanged at all follow-up time points.

Absolute values of the outcomes at baseline and 2 years after TKA are shown in Table II, and the other time points are shown in Appendix Supplementary table i. Absolute values of the outcomes did not different significantly between the 2 groups at baseline, 6 months, 1 year, or 2 years after surgery.

The relative changes in the outcomes at 6 months, 1 year, and 2 years after TKA are shown in Table III. The relative changes in the rectus femoris muscle area were significantly greater in the EAA group than in the placebo group at 1 year ($p = 0.02$) and 2 years ($p = 0.01$) after TKA (Fig. 4). Moreover, the relative change

TABLE I Patient Demographics*

Parameter	EAA Group (N = 26)	Placebo Group (N = 26)	P Value
Age at surgery *(yr)*	76.4 ± 8.3	75.2 ± 5.5	0.56
Female sex	19 (73.1)	23 (88.5)	0.29
BMI *(kg/m²)*	25.2 ± 5.2	24.5 ± 2.9	0.53
Body weight *(kg)*	59.2 ± 12.2	56.6 ± 9.0	0.38
Height *(cm)*	153.2 ± 7.2	151.7 ± 8.0	0.48
Right knee	11 (42.3)	16 (61.5)	0.27
Comorbidities			
Hypertension	13 (50)	9 (35)	0.40
Coronary artery disease	4 (15)	2 (8)	0.67
Osteoporosis	2 (8)	2 (8)	0.99
Serum albumin level *(g/dL)*	4.5 ± 0.4	4.5 ± 0.3	0.74
Food preferences: meat-eater	9 (34.6)	11 (42.3)	0.39
Operative time *(min)*	92 ± 11	93 ± 10	0.51

*Values are given as the mean ± standard deviation or as the count with the percentage in parentheses. EAA = essential amino acid, BMI = body mass index.

TABLE II Absolute Values of Parameters at Baseline and 2 Years After TKA*

Parameter	EAA Group (N = 26)	Placebo Group (N = 26)	P Value
At baseline			
Rectus femoris muscle area *(mm²)*	258.0 ± 88.7	305.2 ± 97.2	0.06
Quadriceps muscle strength *(N)*	130.8 ± 66.7	136.3 ± 62.0	0.77
Rectus femoris muscle diameter *(mm)*	17.5 ± 5.4	20.4 ± 5.3	0.06
VAS for knee pain *(points)*	5.0 ± 2.3	5.1 ± 1.8	0.84
6-meter walk *(sec)*	8.0 ± 3.3	7.2 ± 2.1	0.31
Grip strength *(kg)*	20.1 ± 4.4	20.9 ± 7.2	0.65
Knee extension *(deg)*	−5.8 ± 5.7	−4.8 ± 6.2	0.56
Knee flexion *(deg)*	126.8 ± 6.6	124.0 ± 8.9	0.21
Activities of daily living			0.42
Independent walking	19 (73)	22 (85)	
Walking with cane	6 (23)	2 (8)	
Walking with walker	1 (4)	2 (8)	
Using a wheelchair	0 (0)	0 (0)	
KSS 2011 symptoms *(points)*	6.8 ± 5.7	8.3 ± 6.4	0.36
KSS 2011 satisfaction *(points)*	10.1 ± 4.9	11.4 ± 3.6	0.28
KSS 2011 expectations *(points)*	12.3 ± 3.3	13.8 ± 1.7	0.06
KSS 2011 functional activity *(points)*	29.9 ± 16.3	37.6 ± 16.4	0.09
Femorotibial angle *(deg)*	183.5 ± 4.0	183.8 ± 4.4	0.79
At 2 years after TKA			
Rectus femoris muscle area *(mm²)*	326.0 ± 91.53	345.7 ± 97.1	0.47
Quadriceps muscle strength *(N)*	177.9 ± 62.1	157.3 ± 60.7	0.24
Rectus femoris muscle diameter *(mm)*	21.7 ± 4.9	22.5 ± 5.4	0.64
VAS for knee pain *(points)*	29.6 ± 26.8	25.3 ± 25.3	0.56
6-meter walk *(sec)*	6.0 ± 1.8	6.0 ± 1.6	0.96
Grip strength *(kg)*	22.5 ± 4.4	22.5 ± 7.7	0.98
Knee extension *(deg)*	−2.4 ± 3.6	−1.8 ± 4.1	0.58
Knee flexion *(deg)*	123.8 ± 5.3	123.2 ± 10.9	0.81
Activities of daily living			0.70
Independent walking	22 (85)	21 (81)	
Walking with cane	3 (12)	5 (19)	
Walking with walker	1 (4)	0 (0)	
Using a wheelchair	0 (0)	0 (0)	
KSS 2011 symptom *(points)*	19.2 ± 5.0	19.7 ± 5.0	0.71
KSS 2011 satisfaction *(points)*	24.4 ± 6.8	24.2 ± 9.4	0.94
KSS 2011 expectations *(points)*	9.3 ± 3.1	10.0 ± 3.4	0.48
KSS 2011 functional activity *(points)*	67.4 ± 17.1	59.0 ± 17.0	0.08
Femorotibial angle *(deg)*	175.6 ± 0.6	175.5 ± 0.7	0.52
Prosthesis alignment *(deg)*			
α: femoral component alignment in coronal plane	94.3 ± 1.4	94.5 ± 1.4	0.59
β: femoral component alignment in sagittal plane	90.8 ± 1.8	91.0 ± 1.6	0.21
γ: tibial component alignment in coronal plane	2.5 ± 1.6	2.2 ± 1.9	0.29
δ: tibial component alignment in sagittal plane	92.6 ± 3.0	92.9 ± 3.8	0.61

*Baseline was 1 month before the operation. Values are given as the mean ± standard deviation or as the count with the percentage in parentheses. No differences were significant. EAA = essential amino acid, VAS = visual analogue scale, KSS = Knee Society Score.

TABLE III Relative Values of Parameters at 6 Months and 1 and 2 Years After TKA*

Parameter	EAA Group (N = 26) *(%)*	Placebo Group (N = 26) *(%)*	P Value
At 6 months			
Rectus femoris muscle area	102.1 ± 19.0	97.3 ± 20.7	0.46
Quadriceps muscle strength	114.7 ± 48.4	100.1 ± 41.2	0.26
Rectus femoris muscle diameter	114.1 ± 25.4	100.9 ± 20.3	0.09
VAS for knee pain	41.0 ± 42.0	38.0 ± 30.0	0.81
6-meter walk	92.2 ± 21.6	95.5 ± 18.9	0.56
Grip strength	98.4 ± 19.3	119.3 ± 19.8	0.32
At 1 year			
Rectus femoris muscle area	121.7 ± 26.6	104.5 ± 23.0	0.02†
Quadriceps muscle strength	139.0 ± 45.5	115.4 ± 39.6	0.06
Rectus femoris muscle diameter	121.7 ± 20.4	106.3 ± 18.5	0.009†
VAS for knee pain	42.2 ± 59.5	33.1 ± 23.0	0.50
6-meter walk	87.3 ± 20.7	89.1 ± 17.6	0.74
Grip strength	107.6 ± 18.7	103.5 ± 19.1	0.45
At 2 years			
Rectus femoris muscle area	134.0 ± 30.8	113.8 ± 26.7	0.01†
Quadriceps muscle strength	159.3 ± 54.0	125.4 ± 39.8	0.02†
Rectus femoris muscle diameter	126.6 ± 22.8	109.7 ± 19.2	0.009†
VAS for knee pain	30.4 ± 26.8	25.3 ± 25.3	0.56
6-meter walk	80.7 ± 18.9	86.6 ± 17.9	0.26
Grip strength	110.9 ± 21.8	109.3 ± 18.4	0.46

*The baseline value was taken as 100%, and values relative to it are given (e.g., 120% is 1.2 times the baseline). The values are shown as the mean ± standard deviation. EAA = essential amino acid, VAS = visual analogue scale. †Significant ($p < 0.05$).

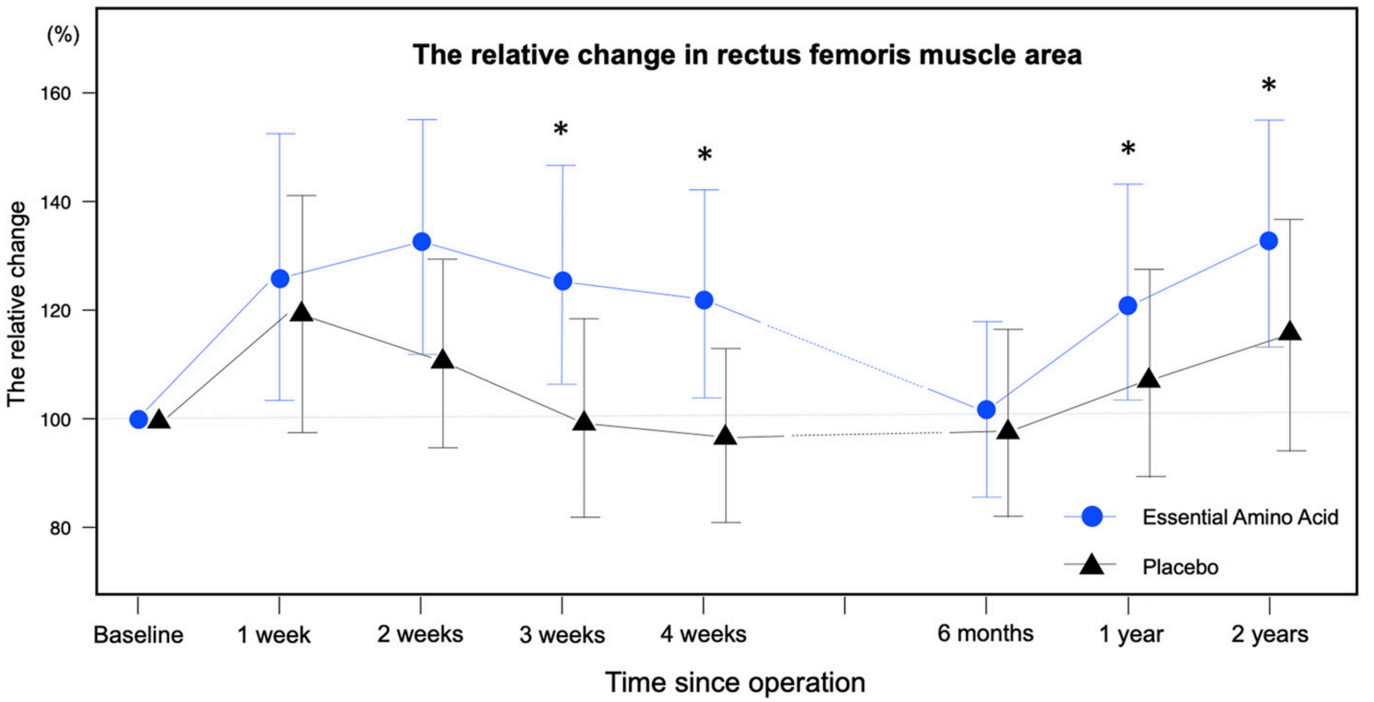

Fig. 4

The relative rectus femoris muscle area (shown as the percentage relative to baseline) at each time point. The baseline value was taken as 100%, and the values relative to that value are shown (e.g., 120% is 1.2×). The recovery of muscle volume was greater in the essential amino acid group compared with the placebo group at 1 and 2 years after surgery. The mean and standard deviation are shown. *Significant ($p < 0.05$).

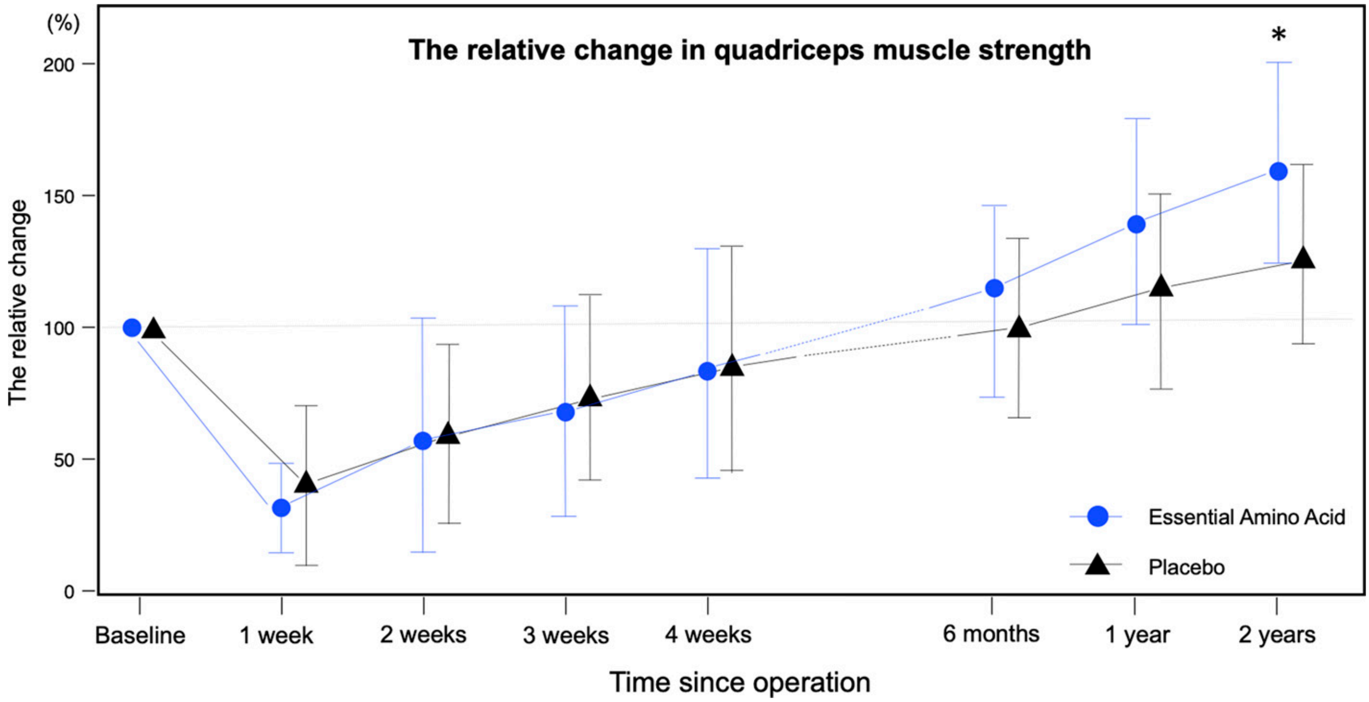

Fig. 5

The relative quadriceps muscle strength (shown as the percentage relative to baseline) at each time point. The baseline value was taken as 100%, and the values relative to that value are shown (e.g., 120% is 1.2×). The recovery of muscle strength was greater in the essential amino acid group compared with the placebo group at 2 years after surgery. The mean and standard deviation are shown. *Significant ($p < 0.05$).

in the quadriceps muscle strength 2 years after TKA was significantly greater in the EAA group than in the placebo group ($p = 0.02$, Fig. 5). The relative changes in the outcomes at 1, 2, 3, and 4 weeks after TKA are shown in Appendix Supplementary table ii.

Multivariate linear regression analysis showed that EAA supplementation was a predictive factor for rectus femoris muscle area recovery at 2 years postoperatively, with a partial regression coefficient of 17.7 (95% CI, 2.2 to 33.2; $p = 0.03$). Age at the time of surgery and sex were also identified as predictive factors, with partial regression coefficients of −1.7 (95% CI, −2.9 to −0.4; $p = 0.01$) per year (a decrease with age) and 35.6 (95% CI, 13.2 to 58.0; $p = 0.003$) for male sex, respectively (Table IV).

TABLE IV Analysis of Factors Predictive of Recovery of Rectus Femoris Muscle Area at 2 Years After TKA*

Variable	Partial Regression Coefficient (95% CI)	P Value
Age at TKA, per year	−1.7 (−2.9 to −0.4)	0.01†
Height, per cm	−0.7 (−2.0 to 0.6)	0.27
Body weight, per kg	−0.7 (−1.5 to 0.1)	0.09
Sex		
Female	Reference	
Male	35.6 (13.2 to 58.0)	0.003†
Supplementation		
Placebo	Reference	
Essential amino acid	17.7 (2.2 to 33.2)	0.03†

*A multiple linear regression model was used and had a p value of 0.002. CI = confidence interval. †Significant ($p < 0.05$).

Discussion

In this study, the rectus femoris muscle area and quadriceps muscle strength were significantly improved from baseline in the EAA group 2 years after TKA. Quadriceps muscle strength in patients who are elderly, as most candidates for TKA are, is positively correlated with functional mobility[17]. Furthermore, the risk of falls[18], cost of patient care[19], and readmission rate after TKA are higher for patients with weak quadriceps muscles[3]. The acceleration of postoperative muscle recovery has the potential to resolve these issues. The results of this study indicate that nutritional intervention may be a clinically important perioperative management strategy in TKA.

Three factors were identified as predictive of greater postoperative recovery of rectus femoris muscle area in this study: EAA supplementation, male sex, and younger age. Previous studies support the roles of all 3 factors. First, skeletal muscle atrophy develops when accelerated catabolism or reduced anabolism causes the rate of muscle degradation to exceed the rate of muscle synthesis[20]. Sufficient perioperative nutritional supplementation has been reported to suppress excessive catabolism due to invasive surgery[21]. EAA supplementation may have buffered excessive postoperative catabolism in our patients in the present study.

Moreover, although invasive surgery results in a short-term increase in catabolism, its metabolic impact has been demonstrated to persist in the long term[22]. The findings of these studies suggest that the prevention of excessive catabolism in the perioperative period can have a continuing favorable effect on muscle mass and strength in the intermediate term after TKA. Second, sex hormones affect muscle volume and strength. Estrogen in women has been demonstrated to have a positive effect on the recovery of muscle volume and strength, but it has less effect on muscle metabolism in older women in whom estrogen has decreased due to menopause[23]. In contrast, although androgen in men declines with age, that change is not as dramatic as the change in estrogen with age in women[24]. Because all of the women in the present study were older than the average age of menopause (approximately 50 years)[25], the lower sex hormone levels in women (but not men) might have affected muscle recovery. Third, muscle volume decreases with age. After the age of 30 years, skeletal muscle mass decreases by approximately 8% per decade[26]. Moreover, skeletal muscle volume is lost more readily in elderly patients than in young ones[27]. Recent basic-science studies have suggested that the slowing of the muscle volume recovery process with age is caused by a reduction in the activity of the basement membrane in muscle fibers[28] and mitochondria in muscle cells[29]. As previously mentioned, sex hormones also decrease with age, which is detrimental to maintenance of muscle volume and strength[24]. Thus, muscle recovery is delayed by many factors in the elderly.

This study demonstrated no differences in patient-reported outcome measurements (PROMs), such as the new KSS 2011, associated with nutritional supplementation. The amount of quadriceps muscle strength change associated with a minimal clinically important difference (MCID) in PROMs in patients with knee osteoarthritis is approximately 4%[30]. The difference in muscle strength in this study (33.9%) far exceeded this MCID, although that cannot be considered definitive because larger changes might be needed to affect PROMs in patients who have undergone TKA. However, the difference in KSS 2011 functional activity in this study, 8.4 points, was considered clinically meaningful because it exceeded the MCID of 4.1 points[31].

It has been reported that quadriceps muscle strength recovers to preoperative levels in approximately 6 months after TKA[32]. However, quadriceps muscle strength recovery was demonstrated to continue beyond 6 months in both groups in the present study, and it became significantly greater than the preoperative level at 2 years after TKA. This result suggests that TKA also permits the eventual recovery of muscle strength that had been lost preoperatively due to osteoarthritis[33]. Quadriceps muscle weakness, as typified by frailty, is closely related to the decline in functional mobility in the elderly[34]. In general, although exercise is important to prevent frailty[34], TKA may also be effective because it results in recovery of muscle strength.

The results involving the absolute values of rectus femoris muscle area and quadriceps muscle strength in the present study should be interpreted with caution. Although the absolute values did not show significant differences between the 2 groups at some of the time points, this may have been because both muscle area and strength were higher in the placebo group than in the EAA group at baseline. Indeed, the relative changes in both values clearly demonstrated the effectiveness of EAA supplementation since these were changes relative to each group's baseline.

This study has limitations. First, although the power analysis determined the number of patients to be sufficient, that number was relatively small. Furthermore, recent advances in computer-assisted TKA may have reduced invasiveness, and minimally invasive techniques have been developed[35,36]. Although it is unclear whether surgical invasiveness could be considered minimal in the present study, the measured muscle atrophy in response to surgery may be smaller than in previous studies. Second, muscle strength was measured isometrically using a handheld dynamometer. Isokinetic measurement is desirable for more detailed evaluations[37]. However, because the ICCs for the muscle strength measurements were good to excellent, we consider the muscle strength data to be reliable. Third, food preferences have been reported to influence daily protein intake[13]. The influence of the lifestyles of the individual patients during the 2-year period of the present study is unknown. However, serum albumin levels and patient food preferences did not differ between the 2 groups, supporting the absence of a bias in daily protein intake during the study. Furthermore, such possible bias would have been minimized by the randomized study design.

In conclusion, the improvements in rectus femoris muscle area and quadriceps muscle strength were significantly greater in the EAA group compared with the placebo group at 2 years after TKA. This indicates that perioperative nutritional intervention could contribute to postoperative muscle recovery not only shortly after TKA but in the intermediate term. There are few clinical studies on quadriceps muscle strength changes before and after TKA. More clinical studies are desirable to investigate quadriceps muscle strength, which is closely related to a patient's functional ability after TKA.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/H363). ■

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