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Effect of Dietary Nitrate Combined With Resistance Training on Postoperative Muscle Function in Sarcopenic Middle-Aged Women Undergoing Knee Osteoarthritis Surgery

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Abstract

Sarcopenia is characterized by the progressive loss of muscle mass and strength. This condition frequently coexists with osteoarthritis (OA) in middle-aged women and often intensifies following surgical procedures. Resistance exercise (RE) is known to help reverse sarcopenia, yet muscle function often remains incomplete in many cases. Supplementation with nitrate (NO_3^-) may offer additional support for muscle repair and work synergistically with RE. The present study evaluated whether adding NO_3^- supplementation to an RE program could better preserve thigh muscle mass and improve strength in middle-aged women during the postoperative rehabilitation phase. A prospective, randomized, placebo-controlled, double-blind trial was conducted involving 36 middle-aged women who had sarcopenia along with cartilage defects and underwent mesenchymal stem cell implantation. Participants were randomly assigned to either the RE plus NO_3^- supplementation group (NG, n = 18) or the RE plus placebo group (PG, n = 18). Both groups participated in a 12-week supervised RE program. Primary outcome measures included thigh muscle cross-sectional area (CSA) and knee strength. Secondary outcomes consisted of functional and clinical assessments, namely the Short Physical Performance Battery (SPPB), skeletal muscle index (SMI), International Knee Documentation Committee (IKDC) score, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. Thigh muscle CSA declined in the PG, whereas it was maintained in the NG. Knee extension strength demonstrated significantly greater gains in the NG compared to the PG at both the 6-week and 12-week time points. Knee flexion strength recovered more rapidly in the NG, with a clear improvement already evident at 6 weeks. The NG also exhibited significant enhancements in SPPB and IKDC scores. In contrast, improvements in WOMAC scores were comparable between the two groups. Combining NO_3^- supplementation with RE proved effective in preventing muscle atrophy and promoting greater strength gains among the participants. These findings suggest that this approach holds promise for optimizing postoperative recovery in this population.

Keywords: Nitrate, Nitric oxide, Beet juice, Sarcopenia, Sarcopenic osteoarthritis, Resistance exercise

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Introduction

Sarcopenia is officially classified as a muscle disease according to the International Classification of Diseases. It is characterized by a steady, ongoing reduction in both skeletal muscle mass and strength. Although its prevalence rises notably in older age groups, the process of muscle

mass reduction begins after age 40. This early decline has substantial negative effects on quality of life, healthcare utilization, and overall morbidity in middle-aged and older adults [1].

A particularly strong link exists between sarcopenia and osteoarthritis (OA), most prominently observed in middle-aged women. Furthermore, diminished thigh muscle mass appears to influence the progression and severity of knee OA to a greater degree than excess body weight [2, 3].

In advanced OA, surgical interventions, such as mesenchymal stem cell (MSC) implantation, are commonly performed. This regenerative strategy is especially appropriate for younger and physically active individuals. It offers distinct advantages over total knee replacement, including a lower likelihood of requiring revision surgery and better preservation of the natural joint architecture [4].

Despite these benefits, the coexistence of sarcopenia can compromise surgical success. It increases the risk of postoperative complications and slows overall healing [5, 6]. In addition, factors such as intraoperative pneumatic tourniquet use and prolonged non-weight-bearing periods contribute to increased muscle catabolism. These elements accelerate the loss of muscle tissue and reduce strength through mechanisms involving inflammation, tissue swelling, and arthrogenic muscle inhibition [7, 8]. Consequently, developing reliable strategies to minimize muscle wasting and safeguard strength is particularly crucial for middle-aged women in this context.

Resistance exercise (RE) has long been recognized as an effective intervention against sarcopenia. It stimulates muscle protein synthesis and leads to measurable improvements in physical capabilities such as walking speed and balance [9]. Nevertheless, postoperative muscle recovery often falls short of expectations, with lingering deficits that can persist for several years. Such prolonged impairments may limit the full restoration of functional capacity and diminish long-term quality of life [10, 11].

Recent research has highlighted the potential of nitrate (NO_3^-) supplementation to facilitate muscle recovery. It appears to achieve this by optimizing muscle contraction efficiency, enhancing nutrient and oxygen delivery, and supporting calcium regulation within muscle cells. NO_3^- may also help alleviate muscle fatigue by improving the utilization of creatine phosphate [12-14]. Despite these encouraging mechanisms, the practical value of NO_3^- supplementation in the specific setting of postoperative rehabilitation—especially when paired with RE—remains unclear. Given the considerable obstacles that sarcopenia creates for successful recovery and functional improvement after OA surgery, it is important to clarify whether NO_3^- can deliver meaningful additional benefits when combined with RE. On this basis, we hypothesized that integrating NO_3^- supplementation with RE during the postoperative period would yield superior improvements in muscle function and clinical outcomes compared with placebo alone in middle-aged women with sarcopenia.

Materials and Methods

Study design and blinding

This investigation was designed as a prospective, randomized, placebo-controlled, double-blind clinical trial. All experimental activities were performed at the Sports Medical Center located within an Orthopedic Hospital (JS Hospital, Seoul, Republic of Korea). Individuals with OA underwent MSC implantation, and every treatment session was administered by therapists who remained separate from the research team.

Similarly, an uninvolved statistician handled the random allocation of participants into groups. Subjects were randomly assigned to the resistance exercise combined with NO_3^- supplementation group (NG) or the resistance exercise combined with placebo supplementation group (PG) using the Research Randomizer program (https://www.randomizer.org/, accessed on 20 October 2023). Thanks to the blinding measures applied throughout the trial, both investigators and participants remained unaware of group assignments. Outcome measurements were collected at the initial assessment and again at 6 weeks and 12 weeks following the intervention period **(Figure 1)**.

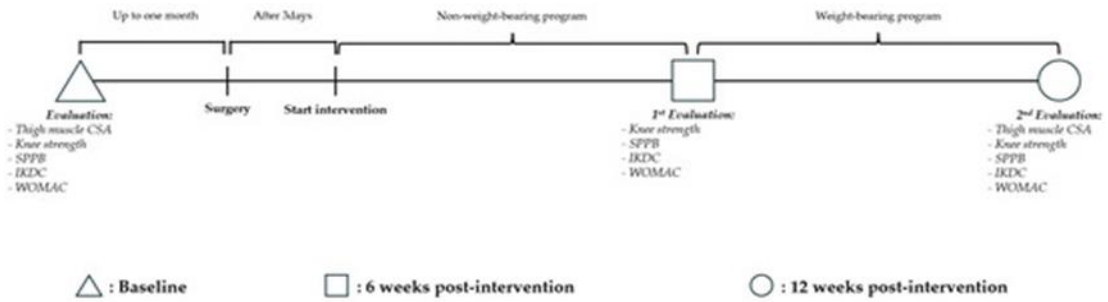


Figure 1. Experimental design. Abbreviations: CSA = cross-sectional area; SPPB = Short Physical Performance Battery; IKDC = International Knee Documentation Committee; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Every aspect of the protocol complied with the ethical principles of the Declaration of Helsinki. Prior approval was granted by the Institutional Review Board of the Korea National Sport University under protocol number 20230621-072. The Clinical Research Information Service also provided official approval for trial registration before any participant was recruited (KCT0008830). Participant flow throughout the study is illustrated in the Consolidated Standards of Reporting Trials diagram presented in **Figure 2**.

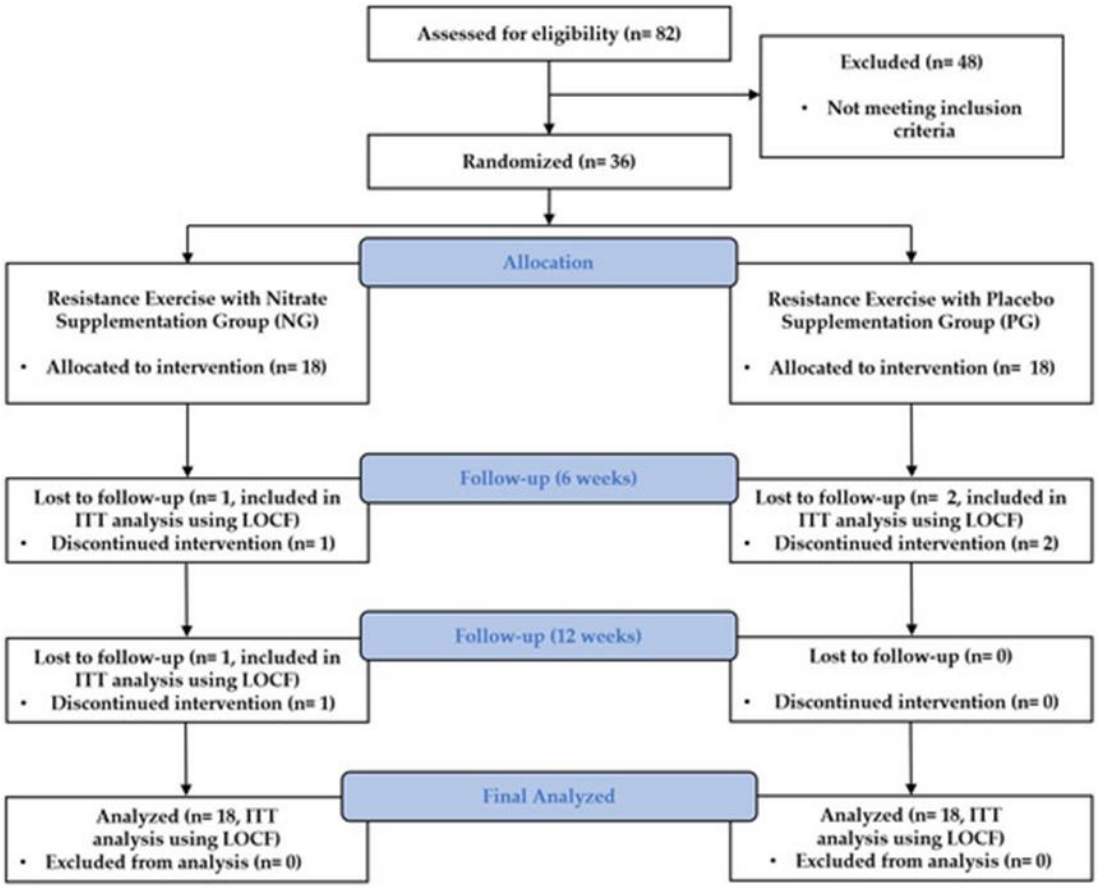


Figure 2. CONSORT flow diagram. LOCF: last observation carried forward; ITT: intent-to-treat.

Participants

Women aged 45 to 65 years who presented with sarcopenia and a confirmed grade IV cartilage defect affecting the medial or lateral femoral condyle, as defined by the International Cartilage Repair Society (ICRS) criteria, were recruited. All selected individuals had MSC implantation planned within the next 1 month. Sarcopenia diagnosis required a skeletal muscle index (SMI) below 5.7 kg/m², handgrip strength below 18 kg, or a score below 9 points on the Short Physical Performance Battery (SPPB).

Participants were excluded if they exhibited severe OA (Kellgren–Lawrence grade 4), had any prior episode of acute coronary syndrome or other cardiovascular conditions, possessed a body mass index reaching 30 kg/m² or more, showed systolic blood pressure values outside 115–160 mmHg, displayed diastolic blood pressure outside 75–100 mmHg, were taking antihypertensive drugs, or regularly consumed nutritional supplements including protein and creatine.

Sample size estimation was performed with G*Power version 3.1.9.2 (Kiel, Germany), setting the desired statistical power at 0.80 and the alpha level at 0.05. The chosen effect size of 0.22 equated to a Cohen's d of 0.44, drawn from earlier data by Seo *et al*. [15] on alterations in midthigh total muscle volume observed in older women with sarcopenia after 16 weeks of resistance exercise. This value was subsequently adjusted to the corresponding F-effect size required for analysis of variance. To compensate for a projected 20% dropout rate, the study aimed to enroll 36 participants, thereby preserving sufficient statistical power to detect significant inter-group differences.

Before participation, all individuals were fully briefed on the aims, procedures, and possible hazards of the study and provided written informed consent.

Intervention

Resistance exercise protocol

Resistance training is recognized as a proven rehabilitation strategy that effectively enhances muscle power and overall physical performance, especially during the recovery period after cartilage restoration procedures. In the current trial, a well-defined RE schedule served as the central element of the protocol, applied equally to both the NG and PG groups [16]. Training began three days following the operation and progressed through two separate stages: a non-weight-bearing (NWB) stage covering the first six weeks and a full-weight-bearing (FWB) stage spanning the following six weeks. Over the entire 12-week period, participants attended 24 guided sessions, held twice per week on set weekdays (Mondays and Thursdays).

The RE schedule was built around three standard sections: a preparatory warm-up, targeted strengthening movements, and a concluding cool-down. In the NWB stage, exercises used Thera-Bands with increasing resistance, starting with a light yellow band and progressing to a medium red band based on each person's reported effort level. The main strengthening work focused on key lower-extremity muscles, including the quadriceps and hamstrings, with careful stepwise increases in effort, repetitions, and resistance.

During the FWB stage, exercises moved to resistance machines and included leg presses, squats, lunges, and hamstring curls. Adjustments to repetitions and resistance loads were made progressively to suit each participant's growing ability to bear full body weight. In addition, specific balance and proprioceptive drills were added in this stage to promote improved functional control.

Warm-up and cool-down segments stayed uniform throughout both stages. Detailed information on every exercise, intensity settings, movement rhythm, and repetition counts appears in **Table 1**.

Table 1. Resistance exercise intervention programs.

Phase	Stage	Exercise	Reps/Duration	Cadence	Intensity (OMNI Scale)
NWB Phase (0–6 weeks)	Warm-up	Upper Body Cycle (UBC)	5 min	–	–
		Stretching	10 min	–	–
	Strengthening	Quadriceps/Hamstring (Q/H) setting	10 s × 10 reps	–	–
		Four-direction Straight Leg Raise (SLR)	10 s × 10 reps	–	–
		Knee extension with Thera-band (yellow/red)	12 reps × 5 sets (by 3 weeks); 8 reps × 4 sets (by 4–6 weeks)	Moderate	4–6
		Hamstring curl with Thera-band (yellow/red)	—	Moderate	4–6
	Additional exercises	Ankle dorsiflexion/plantarflexion with Thera-band (yellow/red)	12 reps × 5 sets	Moderate	4–6
		Hip abduction/adduction	—	–	–
	Cool-down	Cool-down	5 min	–	–
FWB Phase (6–12 weeks)	Warm-up	Stationary cycling	5 min	–	–
		Stretching	10 min	–	–
	Strengthening	Machine leg extension	12 reps × 5 sets (by 9 weeks); 8 reps × 4 sets (by 9–12 weeks)	Moderate to Slow	4–6
		Machine hamstring curl	—	Moderate to Slow	4–6
		Leg press	—	Moderate to Slow	4–6
		Squat	—	Moderate to Slow	4–6
		Lunge	—	Moderate to Slow	4–6
	Additional exercises	Balance and proprioception training	10 min	–	–
	Cool-down	Cool-down	5 min	–	–

Abbreviations: UBC = upper body cycle; ROM = range of motion; Q/H = quadriceps/hamstring; SLR = straight leg raises; NWB = non-weight-bearing; FWB = full-weight-bearing.

Nitrate supplementation details

Intake of NO_3^- has demonstrated potential to support better muscle performance and faster recovery [17]; however, its usefulness during post-surgical rehabilitation remains unclear. In this trial, beetroot juice served as the consistent delivery method for NO_3^- to maintain uniform

dosing while exploring how this supplement interacts with RE.

Participants in both groups consumed 70 mL of beetroot juice delivering a substantial amount of NO3− (6.5 mmol NO3−, Beet It Sport; James White Drinks, Ipswich, United Kingdom) or an equivalent 70 mL placebo drink with almost no NO3− content (0.04 mmol NO3−, James White Drinks, Ipswich, United Kingdom). Administration was managed by a therapist who had no connection to the research group. Each drink supplied 18 g of carbohydrates (of which 17 g consisted of sugars), 3.7 g of protein, and 0.48 g of salt.

The placebo was produced to be identical to the active drink in terms of external packaging, visual appearance, aroma, and flavor, so that neither the subjects nor the study personnel could tell them apart. Both beverages were taken 2 h before each scheduled RE session. Participants were also instructed to avoid nitrate-rich foods, including beets, celery, and spinach, for 48 h before each supplementation session. Blood plasma nitrate concentrations at their peak after drinking were not tracked in this project, as the main goal was to assess clinical and functional improvements from pairing NO3− with resistance training in the postoperative setting. As a result, later investigations might include pharmacokinetic testing to examine nitrate uptake, its availability in the body, and how these factors relate to any benefits observed.

Primary outcome

Thigh muscle cross-sectional area

The central outcome tracked in this investigation was the change in muscle mass, determined by measuring thigh muscle cross-sectional area (CSA) using magnetic resonance imaging (Sigma TwinSpeed, GE Healthcare, Chicago, IL, USA). Scans were performed with participants lying on their backs, the knee held straight in the scanner and secured with Velcro straps to prevent any knee motion. T2-weighted cross-sectional slices were captured every 8 mm using an echo time of 119 ms, a repetition time of 6120 ms, and a 400 mm field of view displayed on a 512 × 512 matrix. To locate the exact measurement site, the full distance from the greater trochanter to the lateral epicondyle was first established from full-length femoral X-rays. A T2-weighted image was obtained at the exact midpoint (50% of that distance). The actual CSA values were outlined along the outer fascial boundary using the region of interest (ROI) function in the Picture Archiving and Communication System software (Viewrex, TECHHEIM, Guro, Republic of Korea). A qualified radiologist repeated the tracing process twice, allowing a 72-hour gap between the two analyses [18]. Consistency of these repeated measurements was checked with Cronbach's alpha coefficient, and only results above 0.8 were included in the final analysis. Thigh muscle CSA data were collected at the start of the study and again 12 weeks after the intervention ended.

Knee strength

Knee strength represented the additional key primary outcome. Maximal voluntary isometric contraction (MVIC) for both knee extension and flexion was recorded with an isokinetic dynamometer (HUMAC Norm; CSMi, Stoughton, MA, USA). Each participant sat on the testing chair, with the hip bent to 90° and the knee at 60°. The torso and pelvis were firmly stabilized using a seatbelt, while the lower leg was fastened with an ankle strap placed 3 cm above the lateral malleolus of the fibula. The machine's rotation axis was carefully aligned with the lateral epicondyle of the femur. Before maximal efforts, two submaximal practice contractions were completed in both directions with a 5 s pause between them. Strong verbal cues and encouragement were given throughout, and a screen displayed live torque readings. After a 10 s recovery following the warm-up contractions, two separate 5 s maximal isometric efforts were recorded for the knee extensors, separated by another 5 s rest. The identical sequence was then followed for the knee flexors. The strongest value from each pair was retained for analysis and reported as a percentage (%) of peak torque divided by body weight [19]. Knee strength testing was performed at baseline and repeated at 6 and 12 weeks following the intervention.

Secondary outcome

Sarcopenia-related outcomes

Sarcopenia-related measures were examined through two primary indicators: the Short Physical Performance Battery (SPPB) and skeletal muscle index (SMI). These tools together provided a detailed evaluation of physical capacity and muscle mass, delivering a solid overview of sarcopenia status.

The SPPB is an effective instrument for gauging lower-limb performance and a reliable predictor of mobility challenges in everyday tasks [20]. It consists of three components: balance assessment, walking speed, and repeated chair rising. Each component is scored from 0 (poorest) to 4 (best), yielding a maximum total of 12 points.

Balance testing followed this sequence: side-by-side stance, semi-tandem stance, and full tandem stance. Holding the side-by-side or semi-tandem position for 10 s earned 1 point each. The tandem stance awarded 1 point for holding ≥ 3 s and 2 points for holding ≥ 10 s. Inability to sustain the side-by-side position for 10 s resulted in a score of 0.

For the gait speed component, the inability to complete the walk scored 0 points. Timing scores were assigned as

follows: > 8.7 s received 1 point, 6.21–8.7 s received 2 points, 4.82–6.20 s received 3 points, and < 4.82 s received 4 points. The test was repeated twice, and assistive devices such as crutches were permitted.

The repeated chair stand component measured the time required to rise from and return to a seated position five times with arms folded across the chest. Scoring was: > 60 s = 0 points, 16.7–60 s = 1 point, 13.7–16.7 s = 2 points, 11.2–13.7 s = 3 points, and < 11.2 s = 4 points. No verbal encouragement was given so that outcomes reflected true individual effort. The test was halted and scored zero if hand support or a fall seemed likely. Final scores from all three parts were added to create a composite score for analysis. Assessments occurred at baseline and 12 weeks post-intervention. The SPPB demonstrated test-retest reliability of 0.87 and convergent validity (P = 0.015) [20]. SMI was additionally determined via bioelectrical impedance analysis using a body water analyzer (BWA 2.0; InBody Co., Gangnam, Korea). Following the manufacturer's instructions, testing was performed in the morning after a minimum 2-hour fast, with all metallic objects removed. The room temperature was controlled between 20 and 25 °C. Participants rested supine for at least 10 minutes beforehand to stabilize body fluid distribution. Electrodes were attached to both wrists and ankles using clamp-style electrodes, with arms kept 15° away from the torso, no arm-torso contact, thighs separated, and legs positioned at approximately shoulder width. SMI was recorded at baseline and at 6 and 12 weeks after the intervention.

Osteoarthritis-related outcome

Osteoarthritis-related measures focused on knee joint function, symptom severity, and activity restrictions associated with OA. Two established instruments—the International Knee Documentation Committee (IKDC) questionnaire and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)—were employed to capture a broad picture of knee condition and patient-reported status.

The IKDC questionnaire assesses symptoms associated with knee OA or related injuries. It examines overall knee condition, including pain levels, restrictions in routine tasks, and limitations during sports activities due to ligament damage or OA. The tool contains 18 items grouped into three domains: symptoms, sports participation, and knee function. Raw scores are transformed into a 0–100 scale, where 100 represents the absence of symptoms or restrictions. In this study, the normalized score was obtained by dividing the total raw score by the maximum possible value (87) and multiplying by 100. This instrument demonstrated internal consistency of 0.91 and construct validity (P < 0.01) [21].

The WOMAC questionnaire provides a standardized way to evaluate knee OA through pain, stiffness, and functional ability. Elevated scores indicate increased discomfort, stiffness, and difficulty with activities. It comprises 5 pain items (scored 0–20), 2 stiffness items (scored 0–8), and 17 functional limitation items (scored 0–68), for a total possible score of 96. Test-retest reliability values were 0.91 for pain, 0.89 for stiffness, and 0.90 for function, with construct validity of P < 0.01 [22].

Statistical analysis

All data were processed and examined with the Statistical Package for the Social Sciences (SPSS) software for Windows (Version 23.0, IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test served to check whether the data followed a normal distribution. Baseline group equivalence for continuous variables was evaluated using the independent t-test when normality was confirmed, and the Mann–Whitney U test when distributions were non-normal, specifically for knee extensor MVIC and SPPB scores. Fisher's exact test was used for comparisons involving categorical variables. Normally distributed outcome variables were analyzed using a two-way repeated-measures analysis of variance. Sphericity was verified using Mauchly's test; when the assumption held (P > 0.05), standard procedures were applied; otherwise, Wilks' lambda was used. Follow-up pairwise comparisons used simple main effects adjusted by the Bonferroni method. Variables lacking normality, such as knee extensor MVIC and SPPB, were analyzed using generalized estimating equations (GEEs) to examine interaction patterns (e.g., time × group) across repeated assessments. Within-group shifts were tested with the Wilcoxon signed-rank test, while between-group contrasts were tested with the Mann–Whitney U test, both with Bonferroni corrections. Effect magnitudes for the repeated-measures ANOVA and GEE models were quantified with partial eta squared (η^2p) and interpreted using these thresholds: small ($0.01 \leq \eta^2p < 0.06$), medium ($0.06 \leq \eta^2p < 0.14$), and large ($\eta^2p \geq 0.14$). Any missing data due to participant withdrawal were addressed using the last observation carried forward (LOCF) method, thereby maintaining the intent-to-treat (ITT) framework. Under this approach, each missing entry was filled with the most recent available measurement for that particular variable—a threshold of $\alpha < 0.05$ defined statistical significance across all tests.

Results and Discussion

The trial recruited 36 women; nevertheless, two members of the NG withdrew—one after reaching the 6-week point and the other after the 12-week point. In parallel, two members of the PG discontinued participation at the 6-week stage after requesting to end the program. As a result, complete data sets were available for 16 participants in each group.

Baseline measurements occurred on average 8.92 ± 2.71 days before program commencement, while final assessments took place 3.91 ± 2.46 days after program completion. Session attendance proved nearly identical between arms, recorded at 94.79 ± 5.38% for the NG and 94.53 ± 5.43% for the PG (P = 0.892). This high and balanced attendance supported the reliability of group comparisons and reinforced the study's internal validity. Initial participant features displayed close similarity across the NG and PG, with no meaningful statistical differences detected **(Table 2)**.

Table 2. Baseline characteristics (n = 36).

Variable	P-value	Difference (95% CI)	PG (n = 18)	NG (n = 18)
Age (years)	0.928 †	0.11 (−2.35 to 2.58)	59.33 ± 4.00	59.44 ± 3.24
Height (cm)	0.391 †	1.22 (−1.64 to 4.08)	156.71 ± 4.27	157.93 ± 4.04
Body weight (kg)	0.795 †	−0.45 (−3.95 to 3.04)	60.02 ± 4.97	59.57 ± 5.18
Body mass index (BMI, kg/m²)	0.468 †	−0.53 (−2.02 to 0.95)	24.45 ± 1.95	23.92 ± 2.32
KL grade 2 (n, %)	0.700 §	—	5 (27.8%)	4 (22.2%)
KL grade 3 (n, %)	—	—	13 (72.2%)	14 (77.8%)
Right knee involvement (n, %)	0.738 §	—	8 (44.4%)	9 (50.0%)
Left knee involvement (n, %)	—	—	10 (55.6%)	9 (50.0%)
Cross-sectional area (CSA, cm²)	0.281 †	1.72 (−1.47 to 4.90)	75.25 ± 3.90	76.96 ± 5.38
Knee extension MVIC (%)	0.084 ‡	10.09 (−3.52 to 23.71)	61.42 ± 18.45	71.52 ± 21.62
Knee flexion MVIC (%)	0.451 †	3.63 (−6.06 to 13.32)	31.53 ± 12.02	35.17 ± 16.27
Skeletal muscle index (SMI, kg/m²)	0.602 †	0.06 (−0.16 to 0.28)	5.29 ± 0.37	5.35 ± 0.27
Hand grip strength (HGS, kg/f)	0.816 †	−0.14 (−1.40 to 1.11)	14.87 ± 1.69	14.72 ± 2.00
IKDC score (points)	0.621 †	−1.35 (−6.85 to 4.15)	36.28 ± 7.82	34.94 ± 8.40
WOMAC score (points)	0.930 †	−0.76 (−7.90 to 6.38)	50.07 ± 7.55	49.31 ± 12.85
Balance test (points)	0.292 ‡	−0.22 (−0.65 to 0.20)	3.17 ± 0.62	2.94 ± 0.64
Gait speed test (points)	0.486 ‡	0.11 (−0.22 to 0.44)	3.61 ± 0.50	3.72 ± 0.46
Chair stand test (points)	0.575 ‡	−0.17 (−0.72 to 0.38)	1.33 ± 0.84	1.17 ± 0.79
Short Physical Performance Battery (SPPB, points)	0.443 ‡	−0.28 (−0.94 to 0.38)	8.11 ± 0.96	7.83 ± 0.99

Abbreviations: NG = nitrate supplementation group; PG = placebo supplementation group; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; KL = Kellgren–Lawrence; CSA = cross-sectional area; MVIC = maximal voluntary isometric contraction; SMI = skeletal muscle index; HGS = handgrip strength; IKDC = International Knee Documentation Committee; Womac = Western Ontario and McMaster Universities Osteoarthritis Index. Data are expressed as mean ± SD or number (percentage).† Independent t-test. ‡ Mann–Whitney U test. § Fisher's exact test.

Primary outcomes

Thigh muscle cross-sectional area

Analysis of thigh muscle CSA uncovered a notable time × group interaction (P = 0.049, $\eta^2p = 0.11$) together with a clear overall change across time points (P < 0.001). Subsequent post hoc checks indicated that muscle area stayed essentially unchanged throughout the study in the NG. By comparison, the PG displayed a marked decline in CSA by the 12-week follow-up (P < 0.001).

Knee strength

Knee extension MVIC produced a significant time × group interaction (p = 0.028, $\eta^2p = 0.08$) and a strong main effect of time (P < 0.001). Post hoc tests confirmed that extension strength remained substantially greater in the NG relative to the PG at both the 6-week (P = 0.002) and 12-week (P = 0.005) assessments. Still, meaningful strength gains from the starting point to 12 weeks appeared in both arms. For knee flexion MVIC, a significant main effect of time emerged (P < 0.001), although the time × group interaction fell short of significance (P = 0.055, $\eta^2p = 0.08$). Post hoc analysis showed clear improvements in flexion strength in the NG at 6 weeks (P < 0.001) and 12 weeks (P < 0.001). The PG, however, registered a significant gain only by the 12-week measurement (P = 0.004). Complete results for the primary outcomes appear in **Table 3**.

Table 3. Comparison of the primary outcomes.

Outcome	Baseline	Group	12 weeks 6 weeks	Mean difference (95% CI)	Mean difference (95% CI)	Mean change (95% CI)	Mean change (95% CI)

Thigh muscle cross-sectional area (cm²)	76.96 ± 5.38	NG (n = 18)	75.57 ± 6.5	—	3.92 (0.12 to 7.71)	—	−1.39 (−2.94 to 0.15)	—
	75.25 ± 3.90	PG (n = 18)	71.65 ± 4.53	—	—	—	−3.59 * (−5.14 to −2.05)	—
Knee extension maximal voluntary isometric contraction (%)	71.52 ± 21.62	NG (n = 18)	92.24 ± 19.88	74.85 ± 18.15	16.76 * (5.46 to 28.07)	18.98 * (9.01 to 28.96)	22.88 * (15.42 to 30.33)	3.31 (−4.17 to 10.8)
	61.42 ± 18.45	PG (n = 18)	75.48 ± 12.72	55.87 ± 10.20	—	—	15.81 * (8.36 to 23.27)	−6.25 (−1.24 to 13.74)
Knee flexion maximal voluntary isometric contraction (%)	35.17 ± 16.27	NG (n = 18)	47.00 ± 11.95	45.67 ± 16.12	7.91 (0.38 to 15.44)	11.24 (1.87 to 20.62)	11.83 * (6.84 to 16.82)	10.50 * (5.96 to 15.04)
	31.53 ± 12.02	PG (n = 18)	39.09 ± 10.22	34.42 ± 11.11	—	—	7.56 * (2.56 to 12.55)	2.89 (−1.65 to 7.43)

Abbreviations: NG = nitrate supplementation group; PG = placebo supplementation group; CI = confidence interval. Data are expressed as mean ± SD. Thigh muscle cross-sectional area and knee flexion maximal voluntary isometric contraction were analyzed using two-way repeated measures analysis of variance, and knee extension maximal voluntary isometric contraction was analyzed using generalized estimation equations. † Mean change (baseline vs. 6 weeks after the intervention); ‡ Mean change (baseline vs. 12 weeks after the intervention); § Mean difference at 6 weeks after the intervention; †† Mean difference at 12 weeks after the intervention. * Significant difference in post hoc analysis.

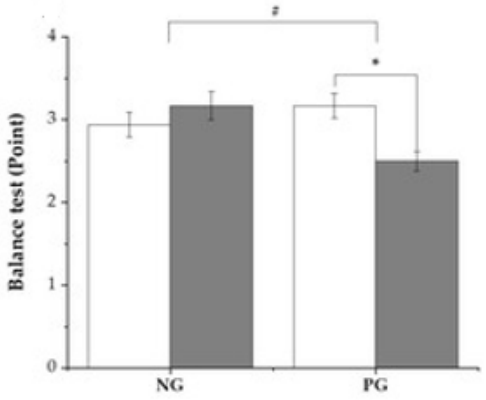
Secondary outcomes

Sarcopenia-related outcome

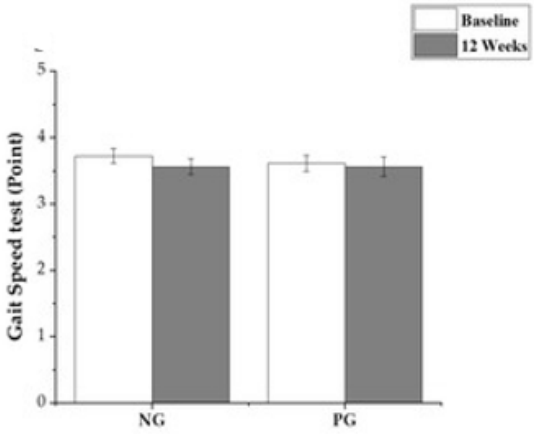
Balance performance on the SPPB exhibited a clear time × group interaction (P = 0.004, η^2p = 0.22), yet the main effect across assessment periods was not significant (P = 0.130). Follow-up tests indicated stable scores in the NG (P = 0.280, Δ: 0.22 [95% confidence interval (CI): −0.19 to 0.63]). Conversely, the PG displayed a notable drop at the 12-week mark (P = 0.002, Δ−0.67 [95% CI: −1.08 to −0.26]).

Gait speed showed no meaningful time × group interaction (P = 0.677, η^2p = 0.01) and no overall change over time (p = 0.407).

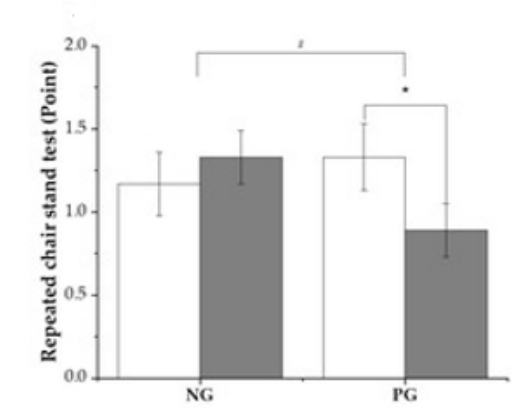
The repeated chair stand component produced a significant time × group interaction (P = 0.040, η^2p = 0.119), although the main time effect remained non-significant (P = 0.337). Post hoc evaluation found no reliable shift in the NG (P = 0.415, Δ: 0.17 [95% CI: −0.24 to 0.58]), while the PG recorded a meaningful decline at 12 weeks (P = 0.035, Δ: −0.44 [95% CI: −0.85 to −0.03]). The total SPPB score also revealed a significant time × group interaction (P = 0.005, η^2p = 0.21) and a significant main effect of time (P = 0.049). Post hoc comparisons confirmed stability in the NG (P = 0.502, Δ: 0.22 [95% CI: −0.44 to 0.89]), but a clear reduction occurred in the PG at 12 weeks (P = 0.001, Δ: 1.17 [95% CI: −1.83 to −0.50]). These SPPB findings are displayed in **Figures 3a–3d**.



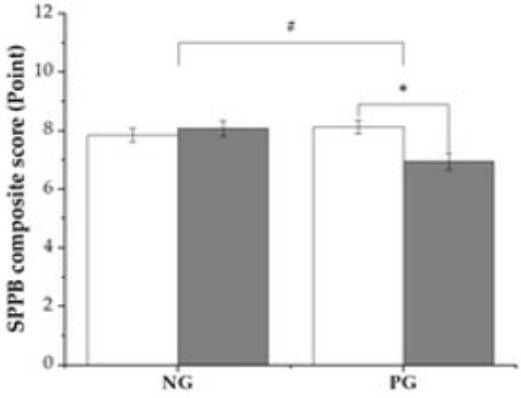
a)



b)



c)



d)

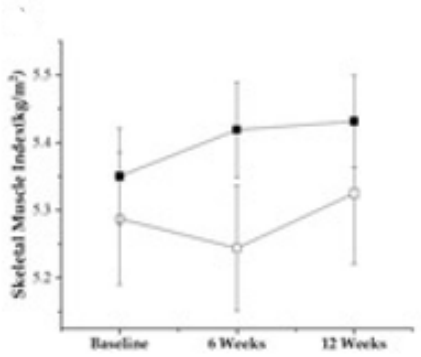
Figure 3. Result of short physical performance battery (SPPB): (a) balance test, (b) gait speed test, (c) repeated chair stand test, and (d) SPPB composite score. Values are expressed as the mean and standard error. * Significant differences within the group; # Interaction effect of time × group by generalized estimation equation.

SMI demonstrated neither a significant time × group interaction (P = 0.253, η^2p = 0.04) nor a significant change across time points (P = 0.194).

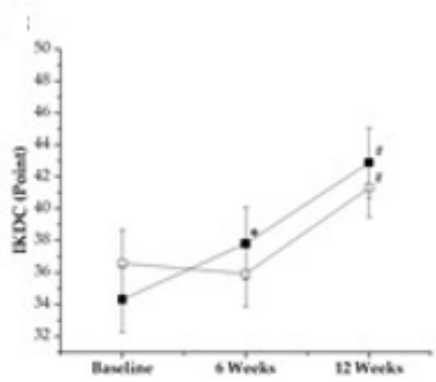
Osteoarthritis-related outcome

IKDC scores produced a significant time × group interaction (P = 0.030, η^2p = 0.2) together with a strong main effect of time (P < 0.001). Post hoc tests showed reliable gains in the NG at 6 weeks (P = 0.047, Δ: 2.24 [95% CI: −0.07 to 4.54]) and at 12 weeks (P < 0.001, Δ: 8.03 [95% CI: 5.67 to 10.38]). The PG, however, improved significantly only by the 12-week assessment (P = 0.001, Δ: 4.04 [95% CI: 1.69 to 6.39]).

WOMAC scores indicated a significant overall change within groups (P < 0.001), but the time × group interaction was not significant (P = 0.244, η^2p = 0.04). Post hoc analysis revealed decreases in both arms at 6 weeks (NG: P < 0.001, Δ: −7.43 [95% CI: −11.07 to −3.78]; PG: P = 0.001, Δ: −6.61 [95% CI: −10.26 to −2.97]) and at 12 weeks (NG: P < 0.001, Δ: −13.93 [95% CI: −18.24 to −9.62]; PG: P < 0.001, Δ: −10.00 [95% CI: −14.31 to −5.69]). Findings for SMI, IKDC, and WOMAC appear in **Figures 4a–4c**.



a)



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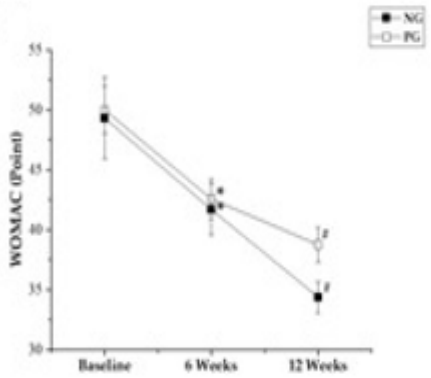

c)

Figure 4. Result of secondary outcome: (a) skeletal muscle index (SMI), (b) International Knee Documentation Committee (IKDC), and (c) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Values are expressed as the mean and standard error. * significant differences from baseline to 6 weeks; # significant differences from baseline to 12 weeks.

The current trial explored how resistance exercise paired with NO3− supplementation affected middle-aged women suffering from sarcopenia after MSC implantation. Results demonstrated that the addition of NO3− helped sustain muscle volume and led to meaningful enhancements in knee extension force. Such outcomes point to improved potential for recovery in the post-surgical phase.

MSC implantation is a reliable and effective method for treating OA, reducing pain and swelling while improving joint mobility [23]. Despite these advantages, the muscle wasting that occurs after the procedure remains a problem. Loss of thigh muscle mass, particularly, increases the risk of falls and balance issues [24]. These difficulties intensify for people with sarcopenia, whose reduced muscle index further limits successful recovery. Earlier work by Liao *et al*. [5] showed that sarcopenic individuals gain less mobility and functional capacity following surgery than those without the condition. For this reason, approaches that limit rapid decline in thigh muscles are vital for restoring everyday movement and strength in affected patients.

Women meeting the Asian Working Group for Sarcopenia standards participated in a resistance exercise program combined with 400 mg NO3− supplementation, aiming to reduce thigh muscle loss after surgery. Data revealed a clear drop in thigh muscle cross-sectional area in the placebo arm, whereas the nitrate group held steady at pre-surgery levels. The preservation of muscle area in the nitrate group appears to be linked to the joint effects of greater muscle recruitment from exercise and the supportive role of NO3−.

Knee extension strength rose in both groups after the program, yet remained considerably higher in the nitrate-supplemented arm at both the 6-week and 12-week checks. Flexor strength also progressed more swiftly in the nitrate group, indicating a stronger overall muscle response to the combined approach. These strength improvements align with earlier reports by Coggan *et al*. [25] and Sim *et al*. [26].

In addition, the exact processes by which NO3− supplementation boosts muscular strength remain unclear. Nevertheless, earlier investigations have provided useful insights. Ferguson *et al*. [27] demonstrated that NO3− specifically improves oxygen delivery to type II muscle fibers, thereby improving metabolic control. Hernández *et al*. [28] further showed that NO3− supplementation increases circulating levels of plasma NO3− and nitrite while also upregulating calcium-handling proteins such as calsequestrin-1 and dihydropyridine receptors, thereby improving contractile performance in type II fibers. Campos *et al*. [29] also highlighted that NO3− reduces the energy cost of ATP consumption, thereby enhancing mitochondrial efficiency and promoting greater blood flow to type II fibers. Collectively, these changes improve muscle contractility and help delay the onset of fatigue. Overall, such mechanisms optimize the delivery of oxygen and nutrients during resistance training, thereby supporting the completion of higher training loads and stimulating muscle protein synthesis [30].

Furthermore, NO3− supplementation increases mechanical tension in muscle tissue. This elevated tension is essential for promoting muscle hypertrophy, as inadequate mechanical loading leads to muscle atrophy, whereas sufficient tension drives muscle growth [31]. Consequently, the reduced muscle atrophy observed in the NG group was most likely due to greater muscle activation and superior strength development compared with the PG group.

Beyond these pathways, nitric oxide plays a key role in limiting muscle damage, facilitating tissue repair, and lowering oxidative stress, all of which are vital for effective muscle recovery [12, 32, 33]. Córdova-Martínez *et al*. [14] observed that combining NO3− supplementation with exercise elevated serum creatinine while reducing total protein levels, which may help protect against sarcopenia by slowing muscle wasting and functional loss [34]. In the current study, resistance exercise paired with NO3− supplementation appears to have prevented muscle atrophy and enhanced strength mainly by improving muscle recruitment patterns rather than by inducing hypertrophy. This interpretation is supported by Esen *et al*. [35], who reported greater activation of the vastus lateralis muscle following NO3− intake. Future research should therefore explore these underlying processes in greater depth through detailed biomarker measurements.

Sarcopenia-related parameters were also examined as secondary outcomes. Osteoarthritis is often accompanied by loss of skeletal muscle mass, a well-established independent risk factor for sarcopenia [36]. Regarding the Short Physical Performance Battery (SPPB), the NG group showed no significant change in overall scores from baseline to 12 weeks. In contrast, the PG group experienced a decrease of 1.17 points. This reduction is clinically important because it exceeds the accepted minimal clinically important difference (MCID) range of 0.5–1.0 points [37, 38] and likely indicates worsening physical function in the PG group. The decline in SPPB performance in the PG may have been partly due to weaker knee extensor strength during the early phase of the program, which negatively affected balance and repeated chair rises. However, by the end of 12 weeks, knee extensor strength in the PG had recovered to baseline levels, possibly preventing further functional deterioration. This partial recovery appeared to be an indirect benefit of the resistance exercise program, although the gains were slower and less consistent than those seen in the NG group. The sustained improvement

in knee extensor strength throughout the intervention in the NG group, aided by NO3− supplementation, probably helped maintain stable SPPB scores and supported continued functional independence [39, 40]. Future studies should therefore investigate whether extending the intervention duration or increasing the NO3− dose could produce measurable enhancements in physical function.

Skeletal muscle index (SMI) remained stable in both groups, which may be explained by the positive influence of resistance exercise on muscle mass and function, consistent with previous work by Beaudart *et al*. [41]. However, NO3− supplementation did not result in a significant increase in SMI. This lack of change is probably due to the relatively brief intervention period, which is generally too short to produce substantial increases in muscle mass, since noticeable hypertrophy usually requires more prolonged training. Additionally, the study did not control dietary protein consumption, which may have restricted potential gains in SMI, as adequate intake of protein and essential amino acids is necessary for muscle protein synthesis. In comparison, Liao *et al*. [5] found that resistance exercise combined with leucine-enriched protein supplementation improved SMI in older adults with osteoarthritis. These results emphasize the important role of dietary protein and essential amino acids in supporting muscle mass development, in agreement with McKendry *et al*. [42]. Based on this evidence, future trials should examine the combined use of NO3− supplementation and increased protein intake to determine whether their interaction can more effectively increase muscle mass.

For osteoarthritis symptoms assessed as secondary outcomes, IKDC scores in the NG group improved significantly at both 6 weeks and 12 weeks after the intervention. In the PG group, however, significant improvements occurred only at the 12-week mark. These results suggest that the quicker gains in knee strength achieved with NO3− supplementation likely contributed to the earlier and greater improvements in IKDC scores observed in the NG group. Knee strength is a strong predictor of performance on functional mobility tests, including the modified physical performance test and the 6-minute walk test [43]. Knee extensor strength has also been linked to stair-climbing ability [44]. At 12 weeks, the NG group showed an 8.03-point increase in IKDC scores, which approached but did not quite reach the minimal clinically important difference of 9.8 points established for knee osteoarthritis populations [45]. The relatively modest improvement may be related to the short duration of the intervention in this study. Therefore, longer intervention periods might be needed to cross clinically meaningful thresholds.

Nevertheless, the early significant improvements in the NG group indicate that adding NO3− supplementation to resistance exercise can accelerate functional recovery during the postoperative phase. By comparison, the PG group recorded a 4.04-point improvement at 12 weeks. Although statistically significant, this change remained below the MCID threshold, suggesting a slower, more gradual recovery.

Improvements in WOMAC scores occurred in both groups, but the difference between them did not reach statistical significance. This outcome indicates that short-term relief from OA symptoms, particularly pain, stems mainly from the surgical procedure itself rather than from changes in muscle mass or strength. Song *et al*. [23] observed marked enhancements in IKDC and WOMAC scores two years after MSC implantation, during which cartilage defects initially classified as ICRS grade IV advanced to grades I and II. These results emphasize the substantial role surgical techniques play in reducing postoperative pain and related complaints. In the present trial, WOMAC scores dropped by 13.93 points in the NG after 12 weeks, narrowly missing the MCID threshold of 16.1 points [46]. By comparison, the PG showed a more modest reduction of 10.00 points, which also remained below the MCID. Nevertheless, both groups reported clear symptom relief. Overall, the data suggest that achieving clinically meaningful WOMAC improvements aligned with MCID standards may require an extended intervention timeframe or the addition of further supportive therapies.

This investigation delivers novel evidence regarding the value of pairing NO3− supplementation with resistance exercise (RE) to optimize recovery after MSC implantation for OA in middle-aged women affected by sarcopenia. The outcomes show that this dual strategy effectively prevents muscle atrophy while strengthening knee extensors, a factor vital to successful rehabilitation. Although earlier work has documented the advantages of NO3− for muscle function and repair, this trial is, to our knowledge, the first to test its combination with RE specifically in the postoperative environment. The implications are especially relevant in light of the common occurrence of sarcopenia and its known negative influence on healing following orthopedic operations, consistent with prior reports on muscle loss and surgical results. Collectively, the study illustrates how NO3− supplementation can be a valuable addition to conventional rehabilitation approaches and underscores the importance of prioritizing muscle strength during the initial recovery phase to accelerate functional progress. Healthcare providers might therefore reduce atrophy risk and promote faster healing by adding NO3− supplementation (400 mg taken 2 h before each session) and RE (2–3 times weekly across 12 weeks) to standard postoperative plans. Such measures could also be adapted for broader community rehabilitation programs,

increasing availability and practicality for a wide range of patients.

Several limitations should be acknowledged in this study. First, because RE and NO3− were supplemented together, separating the specific contribution of NO3− was impossible. Second, the overall intervention length was comparatively brief. Although thigh muscle cross-sectional area served as the main outcome and the combination prevented atrophy in this region, clear evidence of muscle hypertrophy was not detected in the NG; confirming hypertrophy would likely demand a substantially longer protocol. Third, individuals with Kellgren–Lawrence grade IV OA were excluded, limiting the applicability of the findings to those with milder disease severity. This restriction arose from established contraindications for MSC implantation in advanced cases within Korea.

Furthermore, participation was limited to middle-aged women, restricting extrapolation to men, younger adults, or people without sarcopenia. All subjects were postmenopausal, yet precise data on the years elapsed since menopause were not gathered. Because menopausal hormonal shifts can influence muscle tissue and performance, variations in postmenopausal duration might have subtly shaped the results. Subsequent research should therefore record this information to assess its effect on muscle responses better. Fourth, participants' everyday nutritional intake was neither standardized nor tracked, potentially affecting muscle recovery and performance. Subjects were only asked to refrain from nitrate-rich foods, leaving other dietary elements uncontrolled. Future trials would benefit from systematic dietary oversight to limit such variability. Fifth, no blood-based biomarker assessments were conducted, which could have clarified the biological processes behind the observed changes. While muscle strength and cross-sectional area improved, analyzing indicators such as inflammatory cytokines, damage markers, and metabolic signals would have deepened insight into how NO3− supplementation and resistance exercise exert their effects. Lastly, the relatively modest sample size may limit the extent to which the results can be applied. Although the study was initially adequately powered, the loss of 4 participants might have weakened the statistical power. To counteract this, the last observation carried forward (LOCF) approach was used to retain all randomized individuals in the analysis, following intent-to-treat guidelines. Even so, larger future studies will be essential to verify the findings and broaden their relevance.

Conclusion

The results indicate that combining NO3− supplementation with resistance exercise successfully prevented thigh muscle atrophy and boosted muscle strength in the postoperative period. Additionally, the more rapid gains in IKDC scores in the NG imply that NO3− may hasten early functional recovery, primarily by improving knee strength. Overall, this combined intervention shows promise for reducing sarcopenia-associated muscle loss and symptoms while also easing OA-related limitations in joint function and daily mobility. That said, although muscle mass was effectively preserved as indicated by SMI measurements, significant hypertrophy did not develop during the short study period. Secondary measures, such as SPPB scores, must be interpreted cautiously, given the brief intervention window and their correspondingly limited clinical meaning. This strategy offers a practical option for avoiding postoperative muscle wasting and strengthening muscle performance in middle-aged women with sarcopenia, potentially leading to better rehabilitation results and improved quality of life. Still, further investigations over extended periods and across a broader range of OA severity levels are needed to confirm and build on these observations. Ultimately, these findings support the inclusion of NO3− supplementation alongside resistance exercise in sports medicine rehabilitation programs as an innovative tool to aid surgical recovery.

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Conflict of interest: None

Financial support: None

Ethics statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Korea National Sport University (protocol code 20230621-072; date of approval: 21 June 2021).

All participants were informed of the study's purpose, methods, and risks and provided written informed consent.

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