

Preoperative Whey Protein Supplementation and Early Postoperative Outcomes in Older Adults Undergoing Total Hip Arthroplasty

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Abstract

Background

Surgical stress induces metabolic and inflammatory responses that may contribute to postoperative insulin resistance and delayed recovery, particularly in older adults. Preoperative nutritional optimization strategies have been proposed to improve perioperative metabolic stability.

Objective

This randomized controlled trial aimed to evaluate the effects of preoperative whey protein supplementation on early postoperative metabolic markers and recovery quality in older adults undergoing total hip arthroplasty.

Methods

Sixty-two patients aged 50–70 years scheduled for total hip arthroplasty under spinal anesthesia were randomly assigned to either the intervention group ($n = 30$), who received 600 mL of oral whey protein solution six hours before surgery, or the control group ($n = 32$), who received 600 mL of water. Blood samples were collected 24 hours before surgery, immediately before surgery, and 24 hours postoperatively to measure glucose, insulin, HOMA-IR, cortisol, albumin, and C-reactive protein levels. Postoperative recovery quality was assessed using the QoR-15T scale. Analyses were performed using intention-to-treat principles. Between-group comparisons were adjusted for baseline metabolic values using ANCOVA.

Results

Unadjusted analyses indicated lower insulin and HOMA-IR levels in the whey protein group. However, after adjustment for baseline values, no statistically significant group effect was observed for postoperative insulin ($F = 0.98$, $p = 0.327$) or HOMA-IR ($F = 0.969$, $p = 0.002$) levels. No significant differences were observed between groups in glucose, cortisol, CRP, albumin levels, or postoperative recovery quality.

Conclusion

Preoperative whey protein supplementation did not significantly improve early postoperative metabolic or inflammatory outcomes after adjustment for baseline metabolic status. Early postoperative insulin resistance appears to be primarily influenced by pre-existing metabolic conditions rather than a single preoperative whey protein dose.

Highlights

- Preoperative whey protein supplementation did not significantly reduce early postoperative insulin resistance after baseline adjustment.
- Baseline metabolic status was the main determinant of early postoperative insulin and HOMA-IR levels.
- No significant effects were observed on glucose, cortisol, CRP, albumin, or recovery quality.
- A single preoperative whey protein dose may be insufficient to modify short-term postoperative metabolic responses.
- Nutritional optimization strategies may require longer or combined interventions to influence recovery outcomes.

1. Introduction

Aging is associated with progressive physiological and metabolic changes that increase vulnerability to surgical stress and adversely affect postoperative recovery. In elderly individuals, age-related alterations in body composition, reduced muscle mass, and decreased metabolic reserve contribute to an increased risk of malnutrition, impaired immune function, delayed wound healing, and prolonged hospitalization following major surgical procedures. These factors highlight the critical importance of perioperative nutritional status in geriatric patients (1–3). Previous studies have emphasized the importance of preoperative nutritional assessment in elderly surgical patients, demonstrating an association between poor nutritional status, increased postoperative complication risk, and prolonged recovery periods (4). Similarly, other research underscores the need for routine screening of surgical patients for malnutrition risk to inform both preoperative and postoperative nutritional management strategies (5).

Total hip arthroplasty (THA) is one of the most frequently performed orthopedic procedures among elderly individuals and is widely recognized for its effectiveness in relieving pain, restoring joint function, and improving quality of life. However, elderly patients undergoing THA often present with multiple comorbidities and reduced physiological resilience, which may increase susceptibility to postoperative metabolic disturbances, inflammatory responses, and delayed recovery (6).

Preoperative fasting and surgical stress can exacerbate catabolic responses, resulting in increased insulin resistance, elevated stress hormone levels, and accelerated protein breakdown. In elderly patients, these metabolic alterations may negatively influence postoperative recovery and functional outcomes, emphasizing the need for effective nutritional strategies during the perioperative period (7).

Whey protein is a high-quality, rapidly digestible protein rich in essential amino acids and branched-chain amino acids, particularly leucine, which plays a key role in stimulating muscle protein synthesis. Due to its favorable absorption profile and metabolic effects, whey protein supplementation has been proposed as a potential strategy to support metabolic stability and recovery in surgical patients. However, evidence regarding the effects of preoperative whey protein supplementation on postoperative metabolic

markers and recovery outcomes in elderly patients undergoing THA remains limited (8, 9). A meta-analysis reported that whey protein supplementation moderately improved lower-limb muscle strength in older adults and was associated with changes in fasting insulin levels and HOMA-IR values (10). Additionally, comprehensive reviews of the literature suggest that whey protein is a safe and potentially beneficial supplement for improving metabolic health in older adults without underlying renal disease, with evidence indicating possible improvements in insulin resistance, dyslipidemia, vascular function, blood pressure, and chronic low-grade inflammation (11–13).

Therefore, this study aims to evaluate the effects of preoperative whey protein supplementation on postoperative metabolic markers, including cortisol levels, insulin resistance, C-reactive protein, and albumin levels, as well as recovery outcomes in elderly patients undergoing total hip arthroplasty.

2. Method

2.1. Study Design and Setting

This study was conducted as a prospective, open-label, randomized controlled trial. Patients scheduled for total hip arthroplasty were admitted to the orthopedics and traumatology ward one day prior to surgery, and routine preoperative blood tests were performed. All patients were instructed to fast after midnight on the night before surgery and were scheduled as the first case of the day. Surgical procedures were performed under spinal anesthesia and lasted approximately two hours.

The study was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for two-arm randomized controlled trials (14).

2.2. Sample Size Calculation

An a priori power analysis was conducted using G*Power software (version 3.1) to determine the required sample size. As no previous randomized studies had specifically evaluated the effects of preoperative whey protein supplementation in elderly patients undergoing total hip arthroplasty, the effect size was estimated based on a previously published randomized controlled trial examining the metabolic effects of preoperative nutritional loading in surgical patients (15).

Based on this estimation, a minimum sample size of 30 participants per group was required to achieve 90% statistical power with a two-sided alpha level of 0.05 and an assumed effect size of 0.215.

Accordingly, 30 patients were allocated to the intervention group and 32 patients to the control group. A total of 62 patients who met the eligibility criteria were enrolled from the orthopedics and traumatology clinics of a public hospital in Turkey (Fig. 1).

2.3. Randomization

Eligible patients (n = 62) were randomly assigned to either the intervention group or the control group using a computer-generated randomization sequence created through an online randomization tool

(<https://www.randomizer.org/>). Randomization was performed at the time of hospital admission after confirmation of eligibility. This approach ensured that all eligible patients had an equal chance of being allocated to either group and minimized the risk of selection bias.

2.4.Outcomes Measurement

The data for the study were collected using the Individual Demographic Form and the QoR-15T patient questionnaire. The Individual Demographic Form was created by the researchers and through a literature review (16) to record patients' socio-demographic data, as well as blood pressure, pulse, respiratory rate, SpO2 value, blood glucose, cortisol, CRP, albumin, and insulin resistance (HOMA-IR) levels. To assess insulin resistance, the HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) equation ($\text{HOMA-IR} = \text{insulin } (\mu\text{U/mL}) \times \text{glucose (mg/dL)} / 405$) was used (17). The QoR-15T patient questionnaire was developed by Myles PS (18) and was validated for use in Turkish in 2022 (19). The scale scores and subscale scores are compared based on gender, ASA PS, smoking, alcohol consumption, education level, and the scope of surgery. The scale consists of two sections with a total of 15 questions. The first section includes 10 questions regarding how the patient felt during the first 24 hours, while the second section contains five questions related to the patient's experiences in the last 24 hours. This scale is tested by comparing the preoperative and postoperative groups. The measurement is performed using a Visual Analog Scale (VAS) of 100 mm. According to the VAS, scores of 70 mm or lower are considered poor, while scores above 70 mm indicate good postoperative recovery quality. The Cronbach's alpha value for the scale was found to be 0.863. In our study, however, the Cronbach's alpha value of the scale was 0.761.

2.5.Inclusion criteria: Individuals aged 50–70 years who underwent Total Hip Arthroplasty (THA) under spinal anesthesia, had a body mass index (BMI) < 40 kg/m², and were classified as ASA physical status I, II, or III according to the American Society of Anesthesiologists Physical Status Classification System were included in the study.

2.6.Exclusion criteria: Individuals with communication difficulties; diagnosed hepatic, renal, endocrine, gastric, neurological, or psychiatric disorders; malnutrition defined as an NRS-2002 score ≥ 3 ; known allergy to whey protein; or lactose intolerance were excluded from the study. Verbal and written informed consent was obtained from all eligible patients prior to participation, and a written informed consent form was provided in the patient's room.

2.7.Variables of the Study

Independent variables

Age, gender, marital status, educational level, presence of chronic diseases, and duration of surgery.

Control variable

Oral whey protein intake.

Dependent variables

Vital signs (blood pressure, pulse, respiratory SpO2 value), blood glucose, cortisol, CRP, albumin, insulin resistance levels, and postoperative recovery quality scale score.

2.8.Intervention Group

In this study, based on the relevant literature (16, 20) and expert opinions (dietitian, anesthesiologist, and orthopedic surgeon), patients in the intervention group were instructed to consume 600 mL of an oral whey protein solution 6 hours before surgery.

The whey protein solution used in the study was prepared by the researcher by dissolving 60 g of whey protein powder (Katkı Dünyası®, Turkey) in 600 mL of bottled water. The resulting mixture provided approximately 200 kcal and was prepared at room temperature. The solution was administered at the patient's bedside and consumed intermittently over a one-hour period, starting 6 hours before surgery.

Data were collected at three time points: 24 hours before surgery, immediately before surgery, and 24 hours after surgery. For biochemical measurements, 3 mL of venous blood was drawn into appropriate biochemical and hemogram tubes to assess blood glucose, cortisol, albumin, C-reactive protein (CRP), and insulin resistance. All samples were analyzed in the hospital laboratory, and the results were recorded in the Physiological Measurements Table. Postoperative recovery quality was assessed using the QoR-15T questionnaire 24 hours after surgery (Table 1).

2.9.Control Group

Patients in the control group were instructed to consume only 600 mL of water intermittently over a one-hour period, starting 6 hours before surgery. Data collection time points were identical to those of the intervention group: 24 hours before surgery, immediately before surgery, and 24 hours after surgery.

For biochemical measurements, 3 mL of venous blood was collected to evaluate blood glucose, cortisol, albumin, C-reactive protein (CRP), and insulin resistance. Laboratory results were recorded in the Physiological Measurements Table. The QoR-15T questionnaire was administered 24 hours after surgery to assess postoperative recovery quality (Table 1).

Table 1
Application Steps for the Intervention and Control Groups

Application Time	Intervention Group	Control Group
24 Hours Before Surgery	✓ Obtain verbal and written informed consent ✓ Measure vital signs (blood pressure, pulse, respiratory rate, SpO ₂) ✓ Measure blood glucose levels ✓ Measure cortisol, albumin, CRP, and insulin resistance levels	✓ Obtain verbal and written informed consent ✓ Measure vital signs (blood pressure, pulse, respiratory rate, SpO ₂) ✓ Measure blood glucose levels ✓ Measure cortisol, albumin, CRP, and insulin resistance levels
6 Hours Before Surgery	✓ Consume 600 mL whey protein solution	✓ Consume 600 mL water
Immediately Before Surgery	✓ Measure vital signs (blood pressure, pulse, respiratory rate, SpO ₂) ✓ Measure blood glucose levels ✓ Measure cortisol, albumin, CRP, and insulin resistance levels	✓ Measure vital signs (blood pressure, pulse, respiratory rate, SpO ₂) ✓ Measure blood glucose levels ✓ Measure cortisol, albumin, CRP, and insulin resistance levels
24 Hours After Surgery	✓ Measure vital signs (blood pressure, pulse, respiratory rate, SpO ₂) ✓ Measure blood glucose levels ✓ Measure cortisol, albumin, CRP, and insulin resistance levels ✓ Administer QoR-15T questionnaire	✓ Measure vital signs (blood pressure, pulse, respiratory rate, SpO ₂) ✓ Measure blood glucose levels ✓ Measure cortisol, albumin, CRP, and insulin resistance levels ✓ Administer QoR-15T questionnaire

2.10. Statistical Analysis

Categorical variables were summarized as numbers and percentages, whereas continuous variables were expressed as means and standard deviations or medians with interquartile ranges, depending on data distribution. Normality of continuous variables was assessed using the Shapiro–Wilk test.

All analyses were performed according to the intention-to-treat (ITT) principle to preserve the benefits of randomization and minimize potential bias. Participants were analyzed in the groups to which they were originally assigned, regardless of adherence to the intervention protocol.

Baseline characteristics between the whey protein supplementation group and the control group were compared to confirm successful randomization. Between-group comparisons of continuous variables were conducted using independent-samples t-tests or Mann–Whitney U tests, as appropriate, while categorical variables were compared using chi-square or Fisher’s exact tests.

To evaluate postoperative metabolic recovery and inflammatory response over time, repeated-measures analyses were performed across predefined time points (preoperative baseline and postoperative follow-up assessments). Group × time interaction effects were specifically examined to assess whether changes in metabolic markers differed between the intervention and control groups.

Within-group changes over time were analyzed using paired t-tests or Wilcoxon signed-rank tests, whereas between-group differences at each postoperative time point were evaluated using independent-samples tests. For outcomes measured repeatedly over time, generalized linear mixed-effects models were additionally applied to account for intra-individual correlations and missing-at-random data patterns.

Prespecified subgroup analyses were conducted according to age, sex, and baseline nutritional and metabolic status to explore potential effect modification. Interaction terms were tested to assess the consistency of the intervention effect across subgroups.

Effect sizes and relative changes were reported alongside p values to enhance the clinical interpretation of statistically significant findings. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

2.11.Ethical Consideration

The study protocol was approved by the Erciyes University Research Ethics Committee with the decision number: 2023\132 and registered in ClinicalTrials.gov with the identification number NCT06307782. In addition, verbal and written permissions were obtained from the patients included in the research. The data were collected by the researchers and stored securely. The study was conducted according to the guidelines of the Declaration of Helsinki.

3. Results

In the intervention group, 53.3% of patients were male, while 50% of the control group were female. Regarding education level, 46.7% of patients in the intervention group had completed secondary education, compared to 50% of patients in the control group who had completed primary education. All participants were married, and spinal anesthesia was used for all surgeries. There were no statistically significant differences between the intervention and control groups in terms of gender, education level, presence or type of chronic diseases, ASA score, BMI, or duration of surgery ($p > 0.05$) (Table 2).

Table 2
Comparison of Some Characteristics of Patients in the Intervention and Control Groups

Gender	Intervention Group (n = 30)	Control Group (n = 32)	Test a,b	p
Female	14 (46.7)	16 (50.0)	$\chi^2 = 0.069$	p = 0.793
Male	16 (53.3)	16 (50.0)		
Education Level				
Illiterate	1 (3.3)	2 (6.3)	$\chi^2 = 0.734$	p = 0.865
Primary Education	13 (43.3)	16 (50.0)		
Secondary Education	14 (46.7)	12 (37.4)		
Higher Education	2 (6.7)	2 (6.3)		
Chronic Disease				
Present	20 (66.7)	19 (59.4)	$\chi^2 = 0.353$	p = 0.553
Absent	10 (33.3)	13 (40.6)		
Type of Chronic Disease c				
Hypertension	18 (75.0)	17 (68.0)	$\chi^2 = 1.086$	p = 0.581
Heart Failure	6 (25.0)	7 (28.0)		
Chronic Obstructive Pulmonary Disease	0 (0.0)	1 (4.0)		
ASA Score				
II	15 (50.0)	20 (62.5)	$\chi^2 = 0.984$	p = 0.321
III	15 (50.0)	12 (37.5)		
	$\bar{x} \pm sd$	Median [IQR]	$\bar{x} \pm sd$	Median [IQR]
BMI (kg/m²)	28.70 $\pm$ 2.51	29 [3.3]	28.28 $\pm$ 2.51	28.5 [4]
Operation Time (min)	131.00 $\pm$ 14.70	120 [30]	128.43 $\pm$ 13.70	120 [30]
Mann-Whitney U test (Z-table value)				

The mean blood glucose level 24 hours before surgery was similar between the intervention (112 mg/dL) and control groups (123 mg/dL) (p = 0.443). There was no significant difference in glucose levels

between groups at any measured time point.

However, significant differences were observed in insulin and HOMA-IR values. Preoperatively, the mean insulin level was lower in the intervention group (6.9 $\mu\text{U/mL}$) compared to the control group (26.6 $\mu\text{U/mL}$) ($p < 0.001$), and 24 hours postoperatively, insulin remained significantly lower in the intervention group (12.2 $\mu\text{U/mL}$ vs. 28.4 $\mu\text{U/mL}$, $p < 0.001$). Similarly, HOMA-IR values were significantly lower in the intervention group both preoperatively (1.6 vs. 6.3, $p < 0.001$) and 24 hours after surgery (3.7 vs. 8.4, $p < 0.001$), indicating improved insulin sensitivity following preoperative whey protein supplementation (Table 3).

Table 3

Comparison of Glucose, Insulin, and HOMA-IR Values between the Intervention and Control Groups.

	Intervention Group		Control Group		Test*
	(n = 30)		(n = 32)		p
	– X ±S. S.	Median [IQR]	– X ±S. S.	Median [IQR]	
Glucose(mg/dL)					
24 hours before (1)	113.30 ± 25.95	112 [42.5]	121.53 ± 22.32	123 [40.5]	t= -1.341 p = 0.185
Preoperative (2)	97.50 ± 16.46	97 [24.3]	97.13 ± 13.06	97 [15.5]	Z= -0.261 p = 0.794
24 hours after (3)	121.37 ± 15.69	120 [21.5]	125.00 ± 20.83	126 [26]	t= -0.772 p = 0.443
Test, p Difference	F = 18.605, p < 0.001 [2 – 1,3]		χ ² = 29.688, p < 0.001 [2 – 1,3]		
Insulin(μIU/mL)					
24 hours before (1)	30.74 ± 12.94	32 [24.1]	31.32 ± 10.56	33.9 [17.4]	Z= -0.106 p = 0.916
Preoperative (2)	7.60 ± 3.49	6.9 [5.4]	26.20 ± 8.95	26.6 [16.4]	t= -10.892 p < 0.001
24 hours after (3)	12.19 ± 3.07	12.2 [5.7]	27.74 ± 10.00	28.4 [16.7]	t= -8.385 p < 0.001
Test, p Difference	χ ² = 58.067, p < 0.001 [1–2,3] [2–3]		F = 19.233, p < 0.001 [1–2,3]		
HOMA-IR					
24 hours before (1)	8.85 ± 4.70	8.3 [7.9]	9.45 ± 3.75	9.3 [5.5]	t= -0.561 p = 0.577

	İntervetion Group (n = 30)		Control Group (n = 32)		Test* p
	– X ±S. S.	Median [IQR]	– X ±S. S.	Median [IQR]	
Preoperative ⁽²⁾	1.88 ± 1.01	1.6 [1.7]	6.22 ± 2.15	6.3 [3.7]	t= -10.264 p < 0.001
24 hours after ⁽³⁾	3.69 ± 1.15	3.7 [2.2]	8.46 ± 3.15	8.4 [4.7]	t= -8.048 p < 0.001
Test, p	F = 81.353, p < 0.001		F = 37.952, p < 0.001		
Difference	[1–2,3] [2–3]		[2 – 1,3]		

Repeated Measures Test (F-table value),Independent Sample t-test (t-table value),Mann-Whitney U Test (Z-table value),Friedman Test (χ^2 -table value)

No significant differences were observed in cortisol levels between the intervention and control groups at any measured time point ($p > 0.05$).

Albumin levels were similar between groups 24 hours before surgery (intervention: 38.5 g/L vs. control: 37.5 g/L, $p = 0.806$). Postoperatively, albumin was slightly higher in the control group (37 g/L vs. 36 g/L, $p = 0.017$).

CRP levels increased in both groups after surgery, with significantly higher values in the intervention group at 24 hours postoperatively (59.5 mg/L vs. 43.9 mg/L, $p = 0.019$). No significant differences were found preoperatively ($p > 0.05$). (Table 4).

Table 4
Effect Size of Preoperative Whey Protein Supplementation on Variables
(Cohen's d and Partial η^2)

Değişken	Cohen's d (≈)	Partial η^2 (≈)	Yorum
Glucose(mg/dL)	0.20–0.30	0.05	Small effect
Insulin (µIU/mL)	1.5–1.8	0.60 civarı	Very large effect
HOMA-IR	1.3–1.6	0.55–0.70	Very large effect

This table was created to evaluate the effect size of preoperative whey protein supplementation on metabolic parameters. According to the analysis results, preoperative whey protein supplementation had

a large effect size on insulin and HOMA-IR levels (Cohen's $d > 1.0$; partial $\eta^2 > 0.50$). In contrast, a small effect size was observed for glucose levels.

Table 5
Comparison of Cortisol, Albumin, and CRP Values Between the Intervention and Control Groups

	Intervention Group (n = 30)		Control Group (n = 32)		Test* p
	– X ±S. S.	Median [IQR]	– X ±S. S.	Median [IQR]	
Cortisol (µg/dL)					
24 hours before ⁽¹⁾	9.62 ± 5.82	8.2 [8.5]	8.57 ± 3.93	7.9 [6.9]	Z= -0.331 p = 0.741
Preoperative ⁽²⁾	12.19 ± 4.95	12.5 [8.3]	13.28 ± 4.08	14.4 [6.9]	t= -0.938 p = 0.352
24 hours after ⁽³⁾	12.10 ± 5.37	12.4 [8.4]	11.89 ± 3.16	12.4 [3.2]	t = 0.177 p = 0.860
Test, p	χ ² = 5.067, p = 0.079		F = 32.629, p < 0.001		
Difference			[2 – 1,3] [1–3]		
Albumin(mg/L)					
24 hours before ⁽¹⁾	38.17 ± 4.87	38.5 [7]	38.88 ± 4.45	37.5 [6.3]	t = 0.246 p = 0.806
Preoperative ⁽²⁾	35.57 ± 4.46	36.5 [7]	36.44 ± 3.97	36.5 [3.8]	t= -0.812 p = 0.420
24 hours after ⁽³⁾	35.20 ± 3.36	36 [5.3]	37.65 ± 4.39	37 [5]	t= -2.460 p = 0.017
Test, p	F = 41.293, p < 0.001		F = 5.355, p = 0.007		
Difference	[1–2,3]		[2 – 1,3]		
CRP (g/L)					
24 hours before ⁽¹⁾	12.88 ± 15.64	4.2 [15.6]	13.41 ± 11.42	9.1 [21.9]	Z= -0.641 p = 0.522

	Intervention Group (n = 30)		Control Group (n = 32)		Test* p
	–	Median [IQR]	–	Median [IQR]	
	X ±S. S.		X ±S. S.		
Preoperative (2)	28.84 ± 23.51	22.2 [34.6]	27.88 ± 14,66	26.6 [21.7]	Z= -0.704 p = 0.481
24 hours after (3)	59.54 ± 30.37	61 [48.3]	43.94 ± 18.39	42 [28.2]	t = 2.426 p = 0.019
Test, p	$\chi^2 = 60.000, p < 0.001$		$\chi^2 = 56.250, p < 0.001$		
Difference	[1–2,3] [2–3]		[1–2,3] [2–3]		

Repeated Measures Test (F-table value),Independent Sample t-test (t-table value),Mann-Whitney U Test (Z-table value),Friedman Test (χ^2 -table value)

Table 6

ANCOVA-Adjusted Postoperative Insulin and HOMA-IR Levels- Adjustment for baseline (preoperative) values

Outcome	Covariate (Baseline)	Effect	F value	p value
Insulin (24 h postoperative)	Preoperative insulin	Group (Whey vs Control)	0.98	0.327
		Baseline insulin	155.10	< 0.001
HOMA-IR (24 h postoperative)	Preoperative HOMA-IR	Group (Whey vs Control)	0.002	0.969
		Baseline HOMA-IR	94.69	< 0.001

ANCOVA analyses were performed to compare postoperative insulin and HOMA-IR levels between groups while adjusting for baseline (preoperative) values. Group was entered as a fixed factor and baseline values as covariates. After adjustment, no statistically significant group effect was observed for postoperative insulin (F = 0.98, p = 0.327) or HOMA-IR levels (F = 0.002, p = 0.969) (Table X). Baseline insulin and HOMA-IR values were strong predictors of postoperative metabolic outcomes (p < 0.001 for both).

The overall QoR-15T scores decreased in both groups after surgery. Preoperatively, the intervention group had higher scores compared to the control group (84.8 ± 6.54 vs. 81.5 ± 4.33, p < 0.05), while no

significant difference was observed postoperatively (74.2 ± 3.75 vs. 74.8 ± 3.99 , $p > 0.05$). Significant differences were found in individual dimensions, including rest, sleep quality, personal care, comfort and control, and overall well-being ($p < 0.001$), with post-surgery scores generally lower than preoperative scores.

4. Discussion

The findings of this study, which aimed to determine the effects of preoperatively administered whey protein on postoperative cortisol, insulin resistance, CRP, albumin levels, and recovery quality, are discussed below in light of the literature. Although unadjusted analyses suggested lower postoperative insulin and HOMA-IR levels in the whey protein group, ANCOVA analyses adjusting for baseline metabolic values indicated that these differences were no longer statistically significant. This suggests that baseline metabolic status plays a dominant role in determining early postoperative insulin resistance. Given the short postoperative follow-up period of 24 hours, the metabolic effects of a single preoperative whey protein dose may be insufficient to overcome pre-existing insulin resistance in elderly patients undergoing total hip arthroplasty.

Surgical trauma triggers inflammatory, metabolic, and neurohormonal responses. Metabolic disorders, such as insulin resistance, develop after elective surgical procedures and persist for approximately five days postoperatively (21). In addition to calories and carbohydrates, protein plays a crucial role in postoperative recovery as it promotes anabolism, slows muscle catabolism, and shortens the inflammatory phase. Whey protein can be absorbed and utilized by skeletal muscle during stress. Moreover, it stimulates protein synthesis due to its high content of essential amino acids, particularly branched-chain amino acids, which are characterized by high digestibility and rapid absorption in the small intestine (22).

Nevertheless, whey protein is classified as a rapidly digestible protein because it can be readily absorbed and utilized by skeletal muscle during stress and contains essential amino acids, particularly branched-chain amino acids, which are highly digestible and rapidly absorbed in the small intestine (23). Adequate protein intake plays a significant role in postoperative recovery by promoting anabolism, minimizing protein deficits and muscle catabolism, and potentially attenuating the inflammatory response (24).

Studies involving whey protein administration (25, 26, 27) have reported a reduction in patients' blood glucose levels. However, in this study, whey protein was found to have no significant effect on blood glucose levels. Proteins and amino acids found in adequate protein content can reduce insulin response in certain clinical conditions such as obesity and type II diabetes. Whey protein, however, is rich in essential amino acids, which are key regulators of this response, and has been shown to have beneficial effects on HOMA-IR (28). In a study by Onalan et al., which investigated the effects of preoperative oral carbohydrate solution (OCS) administration on postoperative insulin resistance and patient comfort in elective laparoscopic cholecystectomy, OCS was reported to reduce insulin resistance (29). Similarly, Yuan et al. found that administering a preoperative orally enzyme-hydrolyzed rice flour solution to

patients three hours before laparoscopic cholecystectomy significantly reduced postoperative insulin resistance (30). Swanfelt et al. reported that when patients were given a carbohydrate-rich beverage preoperatively, whole-body protein balance was better maintained, and insulin's suppressive effect on endogenous glucose release was preserved more effectively (31).

In our study, HOMA-IR levels were significantly reduced in the group consuming whey protein, demonstrating its effect on insulin resistance. Additionally, 24 hours postoperatively, the HOMA-IR values of patients who consumed whey protein were found to be approximately twice as low as those who consumed only water. Moreover, postoperative insulin resistance remained lower in the whey protein group, with their HOMA-IR values being lower than those in the control group but still above the normal threshold of 2.5 mg/dL. These findings suggest that preoperative administration of carbohydrates, a carbohydrate-whey protein mixture, or carbohydrate-containing fluids can positively impact patients by enhancing satiety and reducing insulin resistance.

In two different studies conducted with orthopedic and THA patients, cortisol levels were found to remain unchanged and within the normal range (32, 33). Similarly, in our study, whey protein administration in the intervention group did not affect cortisol levels. However, since cortisol values remained within the normal range, it can be interpreted that surgical stress did not develop in these patients.

C-reactive protein (CRP) is a widely recognized inflammatory marker, and increases in its plasma concentration correspond to heightened systemic inflammation. In elderly patients undergoing total hip arthroplasty, CRP levels typically rise postoperatively, peaking around the second postoperative day (34).

In a meta-analysis by Akbari et al. evaluating the acute and short-term effects of whey protein supplementation, either alone or in combination with carbohydrates, on inflammatory outcomes, 25 randomized controlled trials were included. The authors reported that whey protein, with or without carbohydrates, did not significantly influence inflammatory markers in the short term (35). Consistent with these findings, our study also demonstrated no significant effect of preoperative whey protein supplementation on postoperative CRP levels, which may be attributable to the dominance of the acute surgical inflammatory response and the limited duration of postoperative follow-up.

Albumin is a well-known marker of protein metabolism, which is often disrupted following trauma such as surgery, sepsis, or burns. The underlying pathophysiology may involve impaired hepatic albumin synthesis in the early postoperative phase, increased basal energy expenditure, and depletion of up to 20% of the body's protein stores. Additionally, capillary leakage, a common feature in sepsis and surgery, leads to albumin sequestration in the third space (36).

Plasma osmotic pressure and serum albumin levels are essential for maintaining physiological functions and serve as key indices for assessing a patient's nutritional status and prognosis. A low serum albumin concentration reduces plasma colloid osmotic pressure and increases the incidence of pleural effusion (37). In one study, a carbohydrate solution mixed with 9 grams of whey protein was administered to

patients three hours before surgery. However, no significant difference was observed in albumin levels between the preoperative and postoperative periods (26). Similarly, Gümüş and Aydın reported that preoperative oral carbohydrate solution administration had no effect on postoperative albumin levels in patients undergoing laparoscopic surgery (38). A study from Northern Tanzania involving patients undergoing major abdominal surgery found that a greater decline in albumin levels was associated with a sixfold increase in the risk of surgical site infections, delayed wound healing, and higher 30-day mortality (adjusted odds ratio: 6.68; 95% CI: 1.59 to 28.09) (36).

In our study, whey protein did not result in a significant difference in albumin levels between groups, and albumin concentrations remained within normal limits in both groups. However, considering that protein catabolism exceeds protein anabolism and may lead to decreased postoperative serum albumin concentrations, it can be suggested that preoperative whey protein intake in elderly patients undergoing THA supports nutritional status and helps maintain postoperative serum albumin levels.

Quality of Recovery (QoR) encompasses various aspects of a patient's daily life after discharge, including physical, psychological, and social well-being, making it a subjective patient experience (39). In a study conducted with painful day-case surgical patients, the postoperative recovery profile over four weeks was found to be low to moderate in the short term (postoperative day 7) and long term (postoperative day 28) (40). In a study by Bescond et al., which aimed to validate the QoR-15 scale for emergency surgery and assess its relationship with postoperative three-month quality of life, a significant difference was observed between early postoperative recovery measured 24 hours after surgery and the QoR-15T score assessed two months later (41). In our study, oral whey protein administration in THA patients did not significantly affect the quality of recovery, and the assessment of the scale 24 hours postoperatively resulted in a lower total QoR score.

The primary strength of this study is that it is the first to demonstrate the effects of preoperative whey protein supplementation on postoperative metabolic recovery and healing in elderly patients. Furthermore, it has been shown to be associated with improved nutritional outcomes, suppression of the acute-phase inflammatory response, and preservation of muscle strength in orthopedic patients. However, this study has certain limitations. The postoperative observation period was limited to 24 hours, which prevented assessment of the long-term effects of preoperative whey protein supplementation; a follow-up study has been planned by the researchers to evaluate these long-term outcomes. Moreover, as this was a single-center study, the generalizability of the protocol to other hospitals may be limited.

5. Conclusions

In this randomized controlled trial, preoperative whey protein supplementation did not significantly improve early postoperative metabolic or inflammatory outcomes after adjustment for baseline values. Baseline metabolic status appeared to be the primary determinant of early postoperative insulin resistance.

Declarations

Declaration of competing interest:

The authors declare no conflict of interest.

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Author Contribution

HY and MB designed and conducted the study. HY performed the statistical analysis, interpreted the findings, and prepared the first draft. MB provided statistical expertise. HY and MB interpreted the results, critically reviewed the draft, and contributed intellectual content. MB supervised the study. All authors are fully responsible for the analysis and interpretation of the data, have read, and approved the final draft.

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Data availability

Data described in the manuscript and analytic code will be made available upon request pending application and approval.

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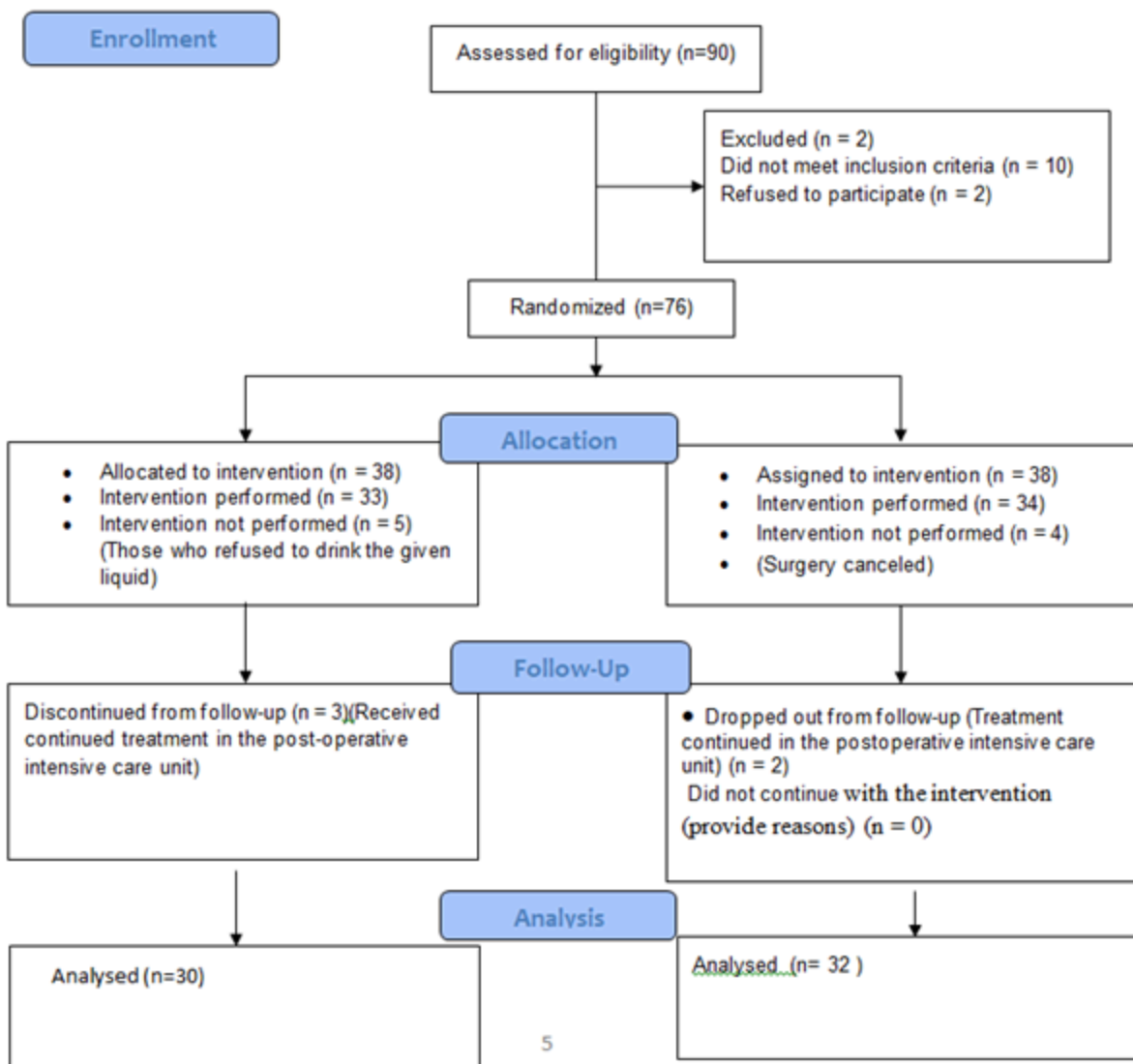
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Figures



5

Figure 1

CONSORT Flow Diagram