Protein Supplement and Enhanced Recovery After Posterior Spine Fusion Surgery

A Randomized, Double-blind, Placebo-controlled Trial

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Study Design: This was a randomized, double-blind clinical trial study.

Objective: The objective of this study was to evaluate the effect of protein supplementation on vertebral fusion and enhanced recovery after posterior spine fusion (PSF) surgery.

Summary of Background Data: Nonfusion is one of the most common complications of lumbar spine surgery. It has been shown that protein plays an important role in bone repair; however, its correlation to vertebral fusion following PSF surgery is unknown.

Patients and Methods: In this randomized, double-blind clinical trial study, the intervention group received a diet with 1.2 g of protein plus high-protein supplement (36 g whey protein), and the control group received a similar diet, except for starch as a placebo from 48 hours before to 1 month after surgery.

Results: The intervention group showed a significantly higher rate of vertebral fusion compared with the control group ($P = 0.019$). Surgical site infection and pain were significantly lower in the intervention group. A significant difference was found in the wound healing rate in favor of the intervention group. The rates of decrease in serum high-sensitivity C-reactive protein levels and increase in serum levels of insulin-like growth factor 1, albumin, total protein, and alkaline phosphatase were greater in the intervention group than in the control group ($P < 0.001$).

Conclusions: Increased protein intake improves vertebral fusion and enhances recovery in patients undergoing PSF. This was the first study to investigate the effect of protein on fusion and healing factors; as a result, further clinical trials are needed to confirm the current results.

Key Words: protein supplement, spine surgery, ERAS

(*Clin Spine Surg* 2021;00:000–000)

Received for publication December 23, 2020; accepted June 1, 2021.

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Studies have shown that in addition to calcium and vitamin D, protein plays an important role in the formation, growth, and maintenance of bone mass. The availability of the required protein is also effective in expanding the fusion mass.[1,2] In addition, several studies have found a positive link between protein intake and increasing bone mineral content and reducing the risk of fractures.[3,4]

By providing structural bone matrix, protein intake optimizes the level of insulin-like growth factor 1 (IGF-1), affects the main elements of bone mineralization (calcium and phosphorus), and affects bone formation and maintenance.[5–9] Clearly, increased protein intake is essential for bone health. Surgery creates catabolic conditions which delay the patient's recovery because of inflammation.[10–13] Moreover, nutritional status is generally impaired and lean body mass is reduced after surgery, followed by increased energy and protein requirements.[14]

Therefore, increased protein intake in spine fusion surgery can affect the fusion of vertebrae by providing structural bone matrix, optimizing IGF-1 levels, increasing intestinal calcium absorption, transporting phosphorus, and improving muscle strength. To our knowledge, no experimental or clinical studies have examined the effect of protein supplementation on vertebral fusion status in spine fusion surgery. This study aimed to determine and compare the effects of protein supplementation before spine fusion surgery until 1 month after surgery on the success rate of vertebral fusion and enhancement of postoperative recovery.

PATIENTS AND METHODS

Study Design and Participants

This randomized, controlled, double-blind clinical trial was conducted in a university hospital, Tehran, Iran. From August 2019 to October 2020, 80 patients who met the inclusion criteria for the study were included. A flowchart of the study is given in Figure 1. Inclusion criteria comprised being scheduled for elective posterior spine fusion surgery, aged 18–65 years, and having a body mass index (BMI) of 18.5–30 kg/m^2. The exclusion criteria were having a history of severe liver disorder, kidney disorder, diabetes, gastrointestinal malabsorption, parathyroid gland disorder, or osteoporosis; smoking; use of

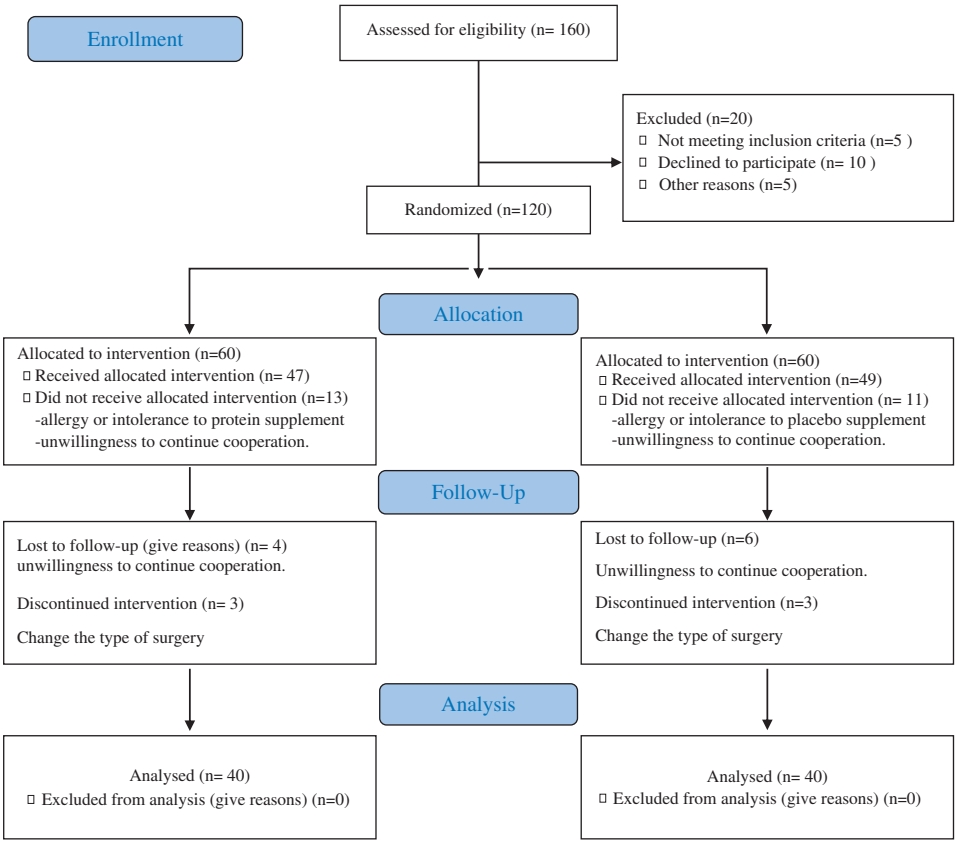

FIGURE 1. CONSORT flow diagram. full color online

medications that affect the metabolism of bone, such as calcitonin, bisphosphonate, or corticosteroid; a history of trauma and fracture of the vertebral; serum level of 25-hydroxyvitamin D $\leq$ 20 ng/L; allergy or intolerance to protein or placebo supplement, and an unwillingness to continue cooperation. The study protocol was approved by the related Ethics Committee and informed consent was obtained from all participants.

Patients were randomized to receive either the intervention or placebo supplement. Supplements in both groups had the same taste and were provided in identical packaging. Patients were randomized by applying a table of random numbers. The patients and investigators were all blinded to the study groups, except the nurse who randomized the patients and prescribed the supplements. Also, by stratified blocked randomization, patients in each group were divided according to their bone mineral density (BMD) into 2 groups: osteopenic (*T*-score greater than negative 2.5) and nonosteopenic (*T*-score greater than negative 1). Regional BMD was measured at the lumbar spine (anteroposterior and lateral views) and the contralateral proximal femur (femoral neck and trochanter).

The intervention group received 36 g/d of whey protein (Karen Pharma and Food Supplement Co., Iran) equivalent to 3 sachets of pure protein 48 hours before surgery. Patients continued to receive the supplement for up to 1 month after surgery.

The placebo group received 3 sachets of starch powder (Karen Pharma and Food Supplement Co.) daily 48 hours before surgery and up to 1 month after surgery.

Patients were excluded from the study if they did not follow the instructions for use (> 10% of supplements not taken). Also, their diets were adjusted with protein in the amount of 1.2 g/kg/d in both groups.

Patients in both groups received the same anesthetic and surgical procedures. A single surgeon performed all posterior spine fusion surgeries.

Outcomes

The primary aim of this study was to assess the rate of vertebral fusion. Secondary aims were to assess rates of surgical site infections, pain, and wound healing as well as levels of IGF-1, high-sensitivity C-reactive protein (hsCRP), albumin, total protein, and alkaline phosphatase.

Clinical, Paraclinical, and Dietary Intake Assessments

In both groups, anthropometric measurements including height, weight, and BMI before surgery, 1, and 3 months after surgery were measured. Patients' nutritional intake was completed at the baseline, 15 days, 1, and 3 months after surgery by 24-hour recall (an average of 3 d: 1 d off and 2 normal days for each time) through an

interview and phone call by the researcher. Nutrition 4 software was used to analyze food intake.

Venous blood samples were taken from patients of each group at baseline and 1 month after surgery to determine the blood levels of IGF-1, albumin, total protein, and alkaline phosphatase and also at baseline, 48 hours, 15 days, and 1 month after surgery to check serum levels of hsCRP. Southampton wound scoring system was used to examine wound at discharge time, 15 days, and 1 month after surgery. Surgical site infection was assessed at 15 days, 1, and 3 months after surgery. Visual Analog Scale was used to evaluate pain in the lower back and pelvis in both groups preoperatively, at the baseline, time of discharge, 15 days, 1, and 3 months after surgery. Computed tomography (CT) scans were used to evaluate the rate of fusion before surgery and 6 months after surgery. A radiologist and neurosurgeon who were both blinded independently interpreted the CT scans. To determine the fusion state in each group and between the 2 groups, Lenke classification was used. In the Lenke classification system, fusion patterns were classified into 4 grades; grades C and D are defined as the nonunion state, and grades A and B are defined as the union state.[15]

Statistical Analyses

Data analysis was performed using SPSS statistical software, version 21. In this study, a P-value < 0.05 was considered as statistically significant. Frequency distribution, mean ± SD, and median (interquartile range) are reported based on the type of variable. The normality of the data was assessed using the Kolmogorov-Smirnov test or histogram chart. The χ^2 test was used to compare qualitative variables between groups. To compare the means of quantitative variables between the studied groups, the t test (if the variable distribution was normal) or the Mann-Whitney test (if the variable distribution was abnormal) was used. The mean of quantitative variables with repetitive measures was done with repeated measure analysis of variance and paired-sample t test. As we did not find a related study about our objective, a true power calculation was not applicable. Thus, we conducted a small pilot study with 12 subjects in each group, to get the estimates needed to do a proper sample size calculation. The minimum sample size estimated for each group was 40 at a power $(1-\beta)$ of 80% and $\alpha = 0.05$ for a 2-arm parallel study with a frequency of 60% and 30% for the rate of vertebral fusion in the protein supplement and control groups, respectively, obtained from a pilot study.

RESULTS

Baseline Characteristics

Of the 96 patients enrolled into the study, 16 patients were lost to follow-up (Fig. 1). Age; sex; BMI; BMD; osteopenia; cause of surgery; level of fusion; preoperative serum levels of vitamin D_3, IGF-1, albumin, total protein, and alkaline phosphatase; and food intake are summarized in Table 1. There were no statistically significant differences in these variables.

TABLE 1. Baseline Characteristic of Patients

Variables	Mean ± SD		
	Intervention (N = 40)	Control (N = 40)	*P*
Age (y)	49.43 ± 8.79	53.18 ± 8.88	0.06*
Sex [n (%)]			
Female	24 (60)	23 (57.5)	0.82†
Male	16 (40)	17 (42.5)	
Osteopenic [n (%)]			
No	24 (60)	23 (57.5)	0.82†
Yes	16 (40)	17 (42.5)	
Serum level of vitamin D_3	28.54 ± 5.61	27.09 ± 4.28	0.56*
Serum level of IGF-1	144.70 ± 51.74	139.77 ± 46.45	0.65*
Serum level of albumin	3.99 ± 0.41	4.06 ± 0.41	0.59*
Serum level of total protein	6.48 ± 0.60	6.44 ± 0.64	0.64*
Serum level of alkaline phosphatase	151.42 ± 44.04	165.27 ± 55.60	0.09*
Level of fusion [median (IQR)]	4 (2)	4 (1)	0.56‡
Cause of surgery [n (%)]			
SS	35 (87.51)	34 (85)	0.74†
SL	5 (12.5)	6 (15)	0.42†
BMI (kg/m^2)			
Baseline	27.09 ± 2.45	26.76 ± 2.07	0.35§ (time)
1 mo after surgery	26.53 ± 2.26	26.92 ± 2.157	0.68 (group)
3 mo after surgery	26.38 ± 2.19	26.93 ± 2.11	
Food intake			
Energy [median (IQR)] (kcal)	2056 (730)	2034.5 (807)	0.82‡
Protein (g)	73.61 ± 13.81	70.56 ± 12.05	0.29*
Carbohydrate (g)	273.50 ± 69.47	298.55 ± 52.38	0.07*
Fat [median (IQR)] (g)	58.3 (19.81)	54.68 (22.84)	0.82‡
phosphorous (mg)	674.81 ± 97.71	640.17 ± 120.52	0.16*
Calcium [median (IQR)] (mg)	403.55 (99.9)	400.25 (125.8)	1‡
Zinc [median (IQR)] (mg)	6.41 ± 0.81	6.44 ± 0.95	0.86*
Magnesium [median (IQR)] (mg)	216.7 (71.7)	231.25 (86.6)	0.18‡
Vitamin K [median (IQR)] (μg)	77.45 (28.77)	79.51 (23.86)	0.82‡
Vitamin C (mg)	64.35 ± 13.77	68.28 ± 9.24	0.13*

*Based on independent samples test.
†Based on χ^2 tests.
‡Based on Mann-Whitney U tests.
§Based on repeated measures analysis of variance.
BMI indicates body mass index; IGF-1, insulin-like growth factor 1; IQR, interquartile range; SL, spondylolisthesis; SS, spinal stenosis.

Fusion

Rate of vertebral fusion had a significant difference between the 2 groups; 7 patients of the intervention group were at level C fusion, but 16 patients of the control group were at level C and D fusion ($P = 0.019$) (Table 2).

Surgical Site Infections

There were no surgical site infections in either group at the time of discharge. However, at 15 days, 1, and 3 months after surgery, the rate of infection was lower in the intervention group than in the control group (Table 3).

TABLE 2. Results of Fusion Assessments Based on Lenke Classification

Variables	n (%) Intervention (N = 40)	Control (N = 40)	P*
Lenke classification			
A (definitely solid)	16 (69.6)	7 (30.4)	0.019
B (possibly solid)	17 (50.0)	17 (50.0)	
C (probably not solid)	7 (38.9)	11 (61.1)	
D (definitely not solid)	0 (0.0)	5 (100)	

*Based on χ^2 tests.

Wound Healing

Rate of wound healing was significantly higher at 15 days and 1 month after surgery in the intervention group ($P < 0.001$) (Table 4).

Pain

Trend reduction in pain was significant in both groups ($P < 0.001$), but it was greater in the intervention group than in the control group. The mean Visual Analog Scale decreased from 8.1 to 0.93 in the intervention group and from 8.7 to 3.1 in the control group ($P = 0.001$) (Fig. 2).

Biochemical

Changes in serum levels of hsCRP were significant over time. A significant difference in the amount of change was observed between the 2 groups; the rate of reduction was greater in the intervention group at 48 hours, 15 days, and 1 month after surgery ($P < 0.001$). Moreover, differences in mean serum levels of IGF-1, alkaline phosphatase, and albumin were meaningful in the intervention group ($P < 0.001$). Overall serum levels increased significantly in both groups compared with before surgery, but the rate of increase was higher in the intervention group after 1 month ($P = 0.046$) (Table 5).

Trend in Food Intake

Postoperative protein, phosphorus, calcium, and zinc intake was higher than preoperative intake, and this increase was the same in both groups. Energy, carbohydrates, and fat intake and the amount of C and K vitamins did not differ between the 2 groups over time (Fig. 3).

TABLE 3. Results of Surgical Site Infection Assessments

Variables	n (%) Intervention (N = 40)	Control (N = 40)	P
15 d after surgery			
Yes	0 (0.0)	6 (100)	0.02*
No	40 (54.1)	34 (45.9)	
1 mo after surgery			
Yes	0 (0.0)	5 (100)	0.049*
No	40 (53.3)	35 (46.7)	
3 mo after surgery			
Yes	1 (2.5)	11 (27.5)	0.03†
No	39 (97.5)	29 (72.5)	

*Based on Fisher exact test.
†Based on χ^2 tests.

TABLE 4. Results of Wound Healing Assessments Based on Southampton Wound Scoring System

Southampton Wound Grade	n (%) Intervention (N = 40)	Control (N = 40)	P*
Discharge time			
0	35 (53.8)	30 (46.2)	
I			
1a	5 (50)	5 (50)	0.76
1b	0 (0.0)	5 (100)	
15 d after surgery			
0	19 (95)	1 (5)	
I			
1a	7 (100)	0 (0.0)	< 0.001
1b	7 (100)	0 (0.0)	
1c	7 (77.8)	2 (22.2)	
II	0 (0.0)	19 (100)	
III	0 (0.0)	16 (100)	
IV	0 (0.0)	2 (100)	
1 mo after surgery			
0	29 (93.5)	2 (6.5)	
I			
1a	4 (80)	1 (20)	
1b	1 (50)	1 (50)	
1c	1 (20)	4 (80)	
II			
2a	0 (0.0)	2 (100)	< 0.001
2b	0 (0.0)	6 (100)	
2c	4 (26.7)	11 (73.3)	
III			
3a	1 (14.3)	6 (85.7)	
3b	0 (0.0)	4 (100)	
3c	0 (0.0)	3 (100)	

Southampton wound scoring system: grade 0 = normal healing, grade I = normal healing+mild bruising, grade II = erythema/tenderness/heat, grade III = clear or haemoserous, grade IV = pus; grade V = deep or severe wound infection.[16]
*Based on Fisher exact test.

DISCUSSION

The results of this study indicated that patients who received protein supplements showed a significantly higher rate in vertebral fusion, lower rates of infection, pain and hsCRP, and higher wound healing and serum levels of IGF-1, albumin, total protein, and alkaline phosphatase.

The primary aim of this study was to determine the rate of vertebral fusion. The results showed that the success rate of vertebral fusion was significantly higher in the intervention group than in the control group.

Enhanced Recovery After Surgery (ERAS) guidelines seek to speed up a patient's recovery by reducing stress responses and neuroendocrines. One of the most important guidelines is to emphasize the patient's nutritional needs before, during, and after surgery with strategies for maintaining nitrogen and lean body mass balance.[17] To achieve a positive nitrogen balance, 1.2–1.5 g/kg/d of protein is required after surgery in patients with normal renal function.[18] In the postoperative period, the patient is in an acute condition and in the anabolic phase for the first 5 weeks after surgery; his protein needs increase during this

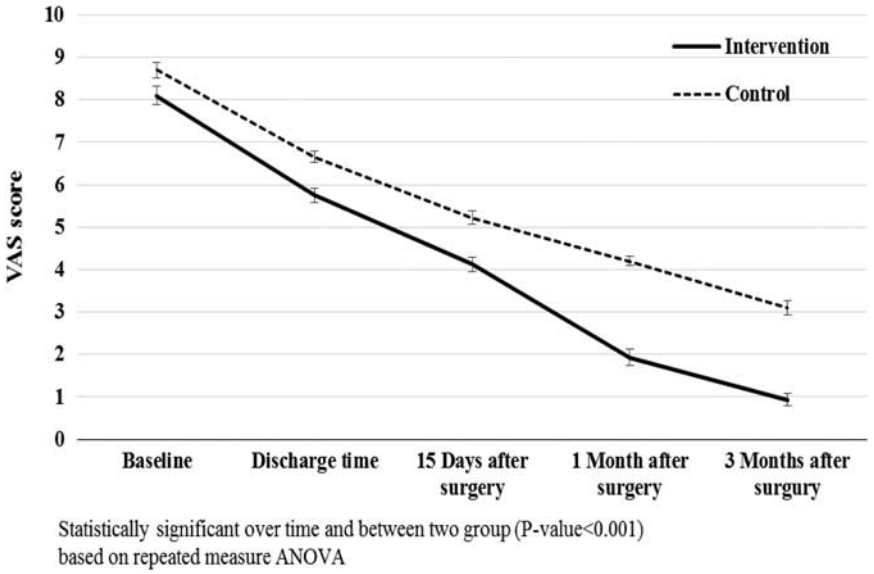

FIGURE 2. Trend of the pain score based on VAS. ANOVA indicates analysis of variance; VAS, Visual Analog Scale.

period.[19] Protein intake is essential for the formation of trabecular bone and cortex, proliferation and differentiation of osteoblasts, and bone anabolism.[8,20,21] Also, many collagen fragments that are proteolized cannot be reused to build new bone matrices. Accordingly, a daily supply of dietary protein is necessary for bone fusion.[22]

TABLE 5. Results of Biochemical Assessments

	Mean ± SD		
Variables	**Intervention (N = 40)**	**Control (N = 40)**	***P***
hsCRP			
Baseline	6.18 ± 3.46	6.10 ± 3.22	< 0.001* (time)
48 h after surgery	17.51 ± 18.47	28.35 ± 17.73	< 0.001 (group)
15 d after surgery	6.92 ± 5.54	17.34 ± 9.78	
1 mo after surgery	2.51 ± 2.08	6.35 ± 5.66	
IGF-1			
Baseline	144.77 ± 51.74	139.77 ± 46.45	0.65†
1 mo after surgery	180.59 ± 39.13	152.13 ± 40.11	0.02†
P‡	< 0.001	0.065	
Albumin			
Baseline	3.99 ± 0.41	3.97 ± 0.39	0.80†
1 mo after surgery	4.76 ± 0.40	4.06 ± 0.41	< 0.001†
P‡	< 0.001	0.18	
Total protein			
Baseline	6.38 ± 0.60	6.44 ± 0.64	0.64†
1 mo after surgery	8.56 ± 0.97	6.61 ± 0.59	0.046†
P‡	0.02	0.02	
Alkaline phosphatase			
Baseline	158.42 ± 44.04	165.27 ± 55.60	0.09†
1 mo after surgery	229.55 ± 52.81	184.65 ± 58.54	< 0.001†
P‡	< 0.001	0.07	

*Based on repeated measures analysis of variance.
†Based on independent samples test.
‡Based on paired- sample *t* test.
hsCRP indicates high-sensitivity C-reactive protein; IGF-1, Insulin-like growth factor.

Fusion rate was assessed by the Lenke classification system. The Lenke classification is a radiologic criterion that is more sensitive to clinical evaluation. Better fusion in CT scan of the intervention group is the higher sensitivity of this test. Clinically, however, a patient may not have the clinical signs of nonfusion and radiologic manifestations, such as a ruptured instrument, and may only have more postoperative pain. Therefore, these results are not far-fetched in the intervention group.

The hsCRP concentrations increase sharply 24–48 hours after tissue injury and gradually decrease until 3 months after surgery.[10] This inflammation delays the patient's recovery through more infection and delayed wound healing.[11,13] Studies have shown that following orthopedic surgery, protein synthesis is inhibited and protein degradation is activated, causing a significant increase in oxidative stress and insulin resistance. Protein administration reduces oxidative stress and inflammatory conditions following surgery.[23] Following a decrease in inflammatory cytokines, hsCRP also decreases. In this study, it was seen that the rate of hsCRP reduction in the intervention group was significantly different from that in the control group. Moreover, following the reduction in inflammation in the intervention group, less infection and more wound healing were seen. The importance of protein in wound healing has been identified and investigated since the early 1930s.[24]

In this study, bone markers such as IGF-1 and alkaline phosphatase were seen to increase more in the intervention group than in the control group. This may be due to the greater bone formation and consequently more fusion mass seen in the intervention group. Restriction of protein intake reduces the plasma level of IGF-1. In addition, high-protein intake can prevent a decrease in IGF-1 in hypocaloric conditions.[6,25] Findings from the study by Schurch et al[26] showed that protein supplementation after

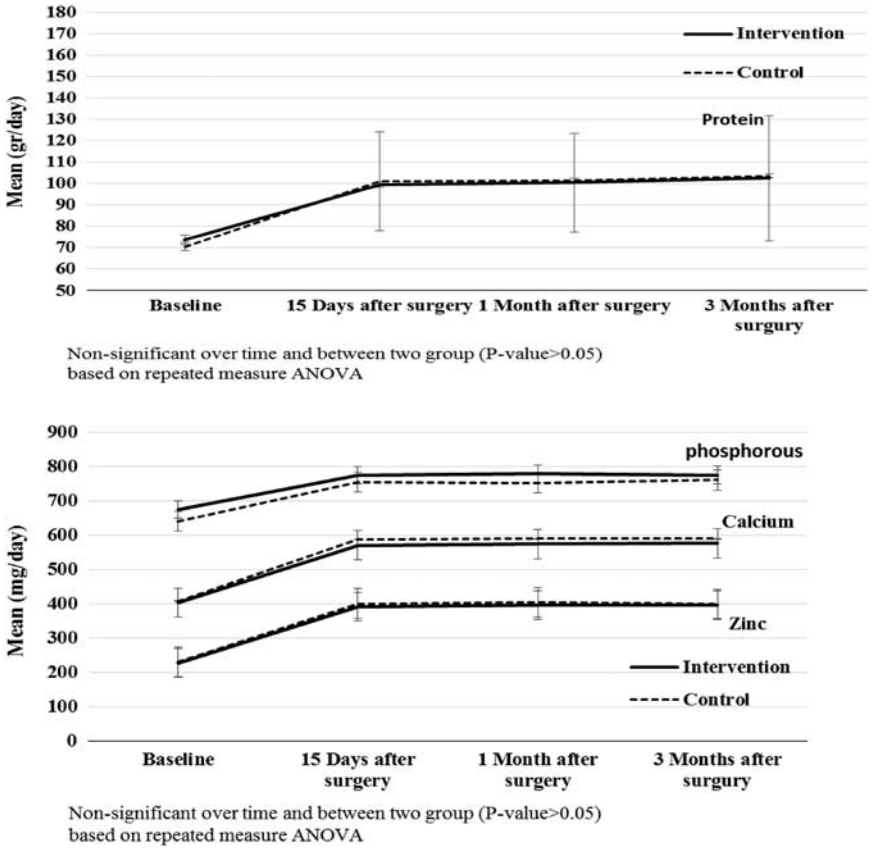

FIGURE 3. Trend in food intakes (protein, phosphorous, calcium, zinc). ANOVA indicates analysis of variance.

hip fracture surgery was associated with increased serum IGF-1 levels and decreased bone loss. In another study, elderly women with hip fractures given oral protein supplements had significant increases in serum IGF-1 in the first week after supplementation.[27]

In this clinical trial, serum albumin and total protein levels were higher in the group receiving protein supplements than in the control group after 1 month. Albumin metabolism is affected by dietary status, and restrictions on protein intake reduce albumin synthesis.[28] In a study by Neumann et al,[29] the administration of high-protein supplements in patients recovering from hip fractures led to significantly higher serum albumin levels and shorter hospital stays in the protein supplement group.

The strengths of this study include the randomized, controlled, double-blind design and the follow-up time in which the effect of protein supplementation was measured up to 6 months after surgery.

Because this was the first study on spine surgery, it had many shortcomings and limitations. First, it was a single-center trial with a small sample size. Second, markers of bone resorption such as collagen I type of telopeptide-C (CTX), hydroxyproline (OHP), pyridinium cross-links (PYD, DPD), and 24-hour urine calcium could not be measured due to lack of facilities. Finally, further studies are required to confirm the effects of protein supplementation shown in the current results.

CONCLUSION

Because protein administration is an effective, safe, and cost-effective treatment for rapid recovery after surgery and successful vertebral fusion in spinal surgery, it seems to be an attractive subject for future studies.

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