Narrative article

Effects of whey protein on the recovery of surgical patients

DOI: 10.5377/alerta.v9i3.23327

Luis Felipe Quintanilla Gutiérrez[1]*, Daniela Rachel Rubio González[2], Ricardo André Quezada Rivera[3], Pablo Ernesto Salazar Colocho[4]

1-4. Dr. Luis Edmundo Vásquez School of Health Sciences, Dr. José Matías Delgado University, Antiguo Cuscatlán, El Salvador.

*Correspondence
luisfquintanillag@gmail.com

1. 0009-0008-4410-1918
2. 0009-0003-0423-746X
3. 0009-0003-5170-952X
4. 0000-0002-8265-5603

Efectos de la proteína de suero de leche en la recuperación de pacientes quirúrgicos

Suggested citation:
Quintanilla Gutiérrez LP, Rubio González DR, Quezada Rivera RA, Salazar Colocho PE. Efectos de la proteína de suero de leche en la recuperación de pacientes quirúrgicos. Alerta 2026;9(3):218-225. DOI: 10.5377/alerta.v9i3.23327

Editor:
Veralís Morán.

Received:
August 20, 2025

Accepted:
July 2, 2026.

Published:
July 31, 2026.

Author contribution:
QGLP[1]: study design and data analysis. RGDR[2]: manuscript design and data or software management. QRRA[3]: literature search and data collection. SCPE[4]: writing, revising, and editing.

Conflicts of interest:
No conflicts of interest..

Abstract
The postoperative complications increased the length of stay by up to 9.7 days, leading to greater discomfort, pain, and suffering for the patient, as well as higher resource consumption and hospital costs. Approximately 18 % of patients undergoing some type of surgical procedure have an inadequate nutritional status. Currently, a multimodal prehabilitation strategy is being developed focusing on addressing nutritional, psychological and physical deficiencies presented by patients, with the aim of reducing potential complications during postoperative period. Among these strategies is supplementation with whey protein. The purpose of this review is to identify the effects of whey protein in multimodal prehabilitation and recovery of post-surgical patients. A literature review was conducted using databases such as SciELO, Elsevier, Pubmed, Springer; Boolean operators such as AND, OR, and NOT were used to optimize the search for studies. Review articles, original research and meta-analyses in English and Spanish, published between 2020 and 2025 were included. Studies have shown positive and favorable results regarding the use of whey protein in multimodal prehabilitation and the recovery of postoperative patients, although more studies are needed to cover all the different types of surgical pathologies.

Keywords
Whey Protein, Postoperative Complications, Length of Stay.

Resumen
Las complicaciones posoperatorias prolongan la estancia hospitalaria hasta 9,7 días, incrementan el sufrimiento del paciente y elevan el uso de recursos y los costos sanitarios. Además, cerca del 18 % de los pacientes quirúrgicos presenta desnutrición, condición asociada con mayor riesgo de complicaciones y recuperación funcional tardía. La prehabilitación multimodal integra intervenciones nutricionales, físicas y psicológicas para optimizar el estado preoperatorio. Entre sus estrategias destaca la suplementación con proteína de suero de leche, por su contenido de aminoácidos esenciales y su capacidad para estimular la síntesis proteica muscular. Se realizó una revisión bibliográfica en PubMed, SciELO, ScienceDirect y SpringerLink con el objetivo de analizar el efecto de la proteína de suero de leche como componente de la prehabilitación multimodal y su contribución a la recuperación posoperatoria. Se incluyeron estudios originales, revisiones y metaanálisis publicados en inglés o español entre 2020 y 2025. La evidencia sugiere que esta suplementación puede favorecer la preservación de la masa muscular, la recuperación funcional y algunos desenlaces posoperatorios. Sin embargo, la heterogeneidad de las intervenciones y poblaciones limita la generalización de los resultados. Se requieren ensayos clínicos que definan dosis, duración y grupos quirúrgicos con mayor probabilidad de beneficio.

Palabras clave
Proteína de Suero de Leche, Complicaciones Postoperatorias, Tiempo de Internación.

Introduction

The term "surgical complication" is used to describe an adverse or unexpected event arising from a surgical procedure.[1] In 1992, Le H, *et al.*, defined a surgical complication as any deviation from the normal postoperative course.[2] Among the most significant postoperative complications are surgical site infections. In the United States, during 2021, these infections were associated with approximately 90,000 hospital readmissions, a mean prolongation of the hospital stay of 9. 7 days, and additional costs to the healthcare system estimated at up to $700 million.[3]

Postoperative pain is one of the most common complications of the perioperative period. In Mexico, a prevalence of moderate to severe pain was observed at 79.5 % at 72 hours, and in Chile at 93 %. In Costa Rica, the prevalence was 80.5 % at 24 hours. Postoperative pain can contribute to delayed mobilization and rehabilitation, prolong suffering, increase the length of hospital stay, and raise the risk of nosocomial infections.[5-7]

Postoperative complications represent a significant factor in patient outcomes; in this context, Chaouch *et al.*, conducted a meta-analysis that included seven studies on patients who underwent hemicolectomy for colon cancer; among the most frequent complications were: surgical site infection, surgical wound dehiscence, intra-abdominal abscesses, urinary tract infection, pneumonia, neurological abnormalities, anastomotic leaks, and hemorrhage.[8]

The traditional perioperative strategy was governed by fasting; clinical practice guidelines in anesthesiology standardly recommend a preoperative fasting period of two hours for clear liquids and six hours for solid foods. Consequently, unnecessarily prolonging this fasting period increases the risk of dehydration, metabolic stress, and insulin resistance in the postoperative period, among other postoperative changes. This state of physiological vulnerability is associated with greater susceptibility to infectious complications, prolonged hospital stays, and an increased risk of mortality.[9,10]

Rollins K *et al.*, proposed changes to the perioperative approach, which would later lay the groundwork for the "Enhanced Recovery After Surgery" (ERAS) protocol, which outlines various interventions across the three phases of surgery: the preoperative, intraoperative, and postoperative stages.[11]

The term "surgical prehabilitation" refers to a process that spans from diagnosis through surgery and consists of one or more preoperative interventions aimed at improving patients' functional capacity and physiological reserve.[12-14]

Multimodal prehabilitation is a perioperative strategy that integrates individualized nutritional interventions, psychological support, and physical exercise programs. Its goal is to optimize the patient's functional, metabolic, and emotional status prior to surgery by reducing modifiable risk factors, such as malnutrition, loss of muscle mass, and decreased strength. Together, these interventions can improve physiological reserve and promote a more favorable postoperative recovery, with the potential to reduce complications, hospital stay, and the morbidity and mortality associated with the surgical procedure.[15]

One of the objectives of the ERAS protocol is to minimize surgical stress, while prehabilitation strategies focus on improving physiological reserve and functional capacity; both strategies complement each other. However, further research is still needed to develop care guidelines that establish criteria for patient selection, timing of intervention, types of surgeries, and other aspects.[16]

Nutrition plays a key role in successful patient recovery, as it is estimated that 18 % of people undergoing surgery have some degree of malnutrition.[17] Unimodal strategies focusing solely on nutrition have been evaluated, and these studies document that adequate nutritional support can reduce the development of complications that may arise during the postoperative period.[18,19]

In 2024, Heus *et al.*, concluded that muscle quality is more important than muscle mass and that, as with other cancer surgeries, there is an association between visceral fat and the risk of postoperative complications. This is because visceral adipose tissue is metabolically active and inflammatory; therefore, it can cause an inadequate response to the surgical procedure.[20]

Whey protein supplementation is one of the nutritional strategies currently used in surgical patients. Studies, such as the one conducted by Mengshi *et al.*, have shown that the use of protein supplements can help reduce pain perception in the postoperative period.[21] Furthermore, it has been found that whey protein supplementation helps reduce the development of muscle atrophy, preserve muscle strength, and shorten rehabilitation time.[22,23]

Currently, there are no clinical guidelines regarding contraindications for whey protein supplementation in surgical patients; similarly, the literature on adverse effects in humans is limited. Cava Edda, *et al.*, in their narrative review, documented effects that could be considered negative or situations in which whey protein should be used under supervision, particularly in individuals with impaired renal or hepatic function or those prone to acne.[24]

Furthermore, whey protein supplementation can be incorporated into multimodal prehabilitation programs. Molenaar C, *et al.*, demonstrated that this strategy is associated with a lower incidence of postoperative and medical complications, as well as better functional recovery compared to standard care. However, despite the advantages of this type of nutritional strategy, its implementation has been found to vary greatly among different healthcare systems worldwide; furthermore, many countries have limited access to prehabilitation protocols

due to the lack of a standardized protocol.[25,26] Consequently, the objective of this study is to identify the effects of whey protein on multimodal prehabilitation and recovery in post-surgical patients.

Discussion

Mechanisms of action of whey protein

One of the main byproducts of the dairy industry is whey, which contains lactose, minerals, vitamin B, and proteins rich in essential amino acids.[27] During cheese production, casein and whey protein are separated; whey is available in various forms, such as whey protein concentrate, whey protein isolate, lactose-reduced whey, partially hydrolyzed whey, and demineralized whey protein. Whey protein is composed of β-lactoglobulin, α-lactalbumin, immunoglobulins, glycomacropeptide, bovine serum albumin, lactoferrin, and lactoperoxidase; because it contains all the essential amino acids, it is considered a complete protein.[28]

Whey protein has been used for the many functions attributed to it, such as antimicrobial, anti-inflammatory, and immune-boosting activity; lowering blood pressure and cholesterol; facilitating bone repair; and increasing muscle mass.[29-31]

Connolly *et al.*, conducted a systematic review of clinical trials, in which they synthesized the evidence on the use of whey protein and its effect on physiological parameters related to risk factors for developing type 2 diabetes *mellitus*. Of the 2964 trials identified, 13 met the inclusion criteria; the findings of this systematic review suggest that whey protein may reduce glycated hemoglobin and fasting insulin, as well as triglycerides and blood pressure, in overweight and obese individuals. However, this same study notes that the dose, duration, and type of whey protein vary across studies.[32]

The effects of whey protein on glycemic control involve glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are incretin hormones with inotropic effects. GIP stimulates insulin release in response to food intake, while GLP-1 acts through a negative feedback mechanism on gastric emptying; this stimulates pancreatic cells, increases insulin secretion, decreases glucagon release from the pancreas, and increases the number and function of pancreatic beta cells responsible for storing and producing insulin. This could help reduce the risk of type 2 diabetes, obesity, or metabolic syndrome.[28]

The antioxidant properties of whey protein have been studied primarily using *in vitro* methods; Corrochano *et al.*, conducted a systematic review, which concluded that certain components, such as beta-lactoglobulin and alpha-lactoglobulin, have demonstrated antioxidant activity. However, this same study concludes that evidence in humans is insufficient and shows inconsistent results.[33]

The meta-analysis by Prokopidis *et al.*, showed that supplementation with whey or soy protein did not result in statistically significant changes in circulating levels of CRP, IL-6, or TNF-alpha compared with the control groups.[34]

Furthermore, through experiments in animal models, studies such as that by Dong Jin Ha *et al.*, determined that the use of whey protein reduces inflammation by decreasing free radicals and through other effects within the immune system mediated by bioactive molecules such as epidermal growth factor, colony-stimulating factor, transforming growth factor alpha and beta, insulin-like growth factor, and fibroblast growth factor. They concluded that this leads to an increase in adaptive immunity, specifically an increase in the production of immunoglobulin G (IgG), B cells, and helper T cells.[35]

Willems E, *et al.*, demonstrated that pretreatment with whey protein protects intestinal cells against oxidative stress caused by inflammatory challenges, achieving a dose-dependent reduction in reactive oxygen species (ROS) or cellular free radicals.[36]

Whey protein as part of multimodal prehabilitation in the development of postoperative complications

Amirkhosravi *et al.* conducted a systematic review and meta-analysis, examining clinical trials of elective abdominal surgeries that implemented multimodal prehabilitation (physical activity, nutritional [with whey protein], or psychological interventions). They found that groups implementing a prehabilitation strategy experienced fewer complications than control groups. They concluded that prehabilitation interventions may have a protective effect against the development of postoperative complications.[37]

Srinivasaraghavan *et al.*, conducted a systematic review and meta-analysis that included clinical trials of cancer patients who underwent surgery and received whey protein supplementation during the perioperative period. The authors concluded that there was a significant reduction in the incidence of postoperative complications in the intervention group (22 %) compared to 32 % in

the control group. However, the authors noted that the lack of standardization in whey protein dosage and heterogeneity among the studies limited the certainty of the evidence, which was rated as moderate to low.[38]

De Carvalho *et al.*, conducted a double-blind, randomized clinical trial in patients undergoing head and neck cancer surgery. They divided the patients into two groups: the intervention group (clear fluids with carbohydrates enriched with whey protein) and the control group (clear fluids with carbohydrates only), with the aim of analyzing nutritional status and the development of postoperative complications. When comparing the two groups, the frequency of complications was lower in the group that received fluids containing carbohydrates plus whey protein ($p < 0.001$)[39].

Khalooeifard *et al.*, conducted a clinical trial in which they divided patients scheduled for spinal surgery into two groups. The intervention group received a diet containing 1. 2 g of protein plus a protein-rich supplement (36 g of whey protein), and the control group received a similar diet, except with starch as a placebo, starting 48 hours before and continuing for one month after surgery. The objective was to evaluate the rate of vertebral fusion, surgical site infections, pain, surgical wound healing, and levels of inflammatory markers. At the time of discharge, no surgical site infections were reported; however, at 15 days, one month, and three months, the infection rate in the intervention group was lower than in the control group. The trend toward pain reduction was significant in both groups, but it was greater in the intervention group than in the control group.[40]

Carli F, *et al.*, conducted a four-year clinical trial in frail patients undergoing colorectal cancer resection. The group was randomly divided; the first group received four weeks of prehabilitation, and the second group received four weeks of postoperative rehabilitation. Both groups underwent a multimodal intervention that included exercise, psychological care, and nutritional supplementation (with a target protein intake of 1. 5 g/kg of body weight); it is important to note that for obese patients, protein requirements were calculated using adjusted weight. In cases where the protein goal was not met through diet alone, whey protein supplementation was administered; this was to be consumed within one hour after strength training.

The primary objective was to compare the two interventions in terms of the development of complications during the first 30 postoperative days. They found that there were no significant differences between the groups in the development of postoperative complications, length of hospital stay, emergency department visits, and readmissions.[41]

Chen J, *et al.*, conducted a single-blind, randomized controlled clinical trial in which they implemented a multimodal prehabilitation program for patients undergoing gastric cancer surgery. The program spanned three weeks and included aerobic and resistance exercise, respiratory training, nutritional supplementation with whey protein, and psychological care. The control group received routine preoperative care. An average of 6. 1 complications was documented in the intervention group, compared to 9. 8 in the control group. The incidence of severe cardiovascular and respiratory complications was lower in the intervention group than in the control group.[42]

The clinical trial conducted by Liu Z, *et al.*, implemented a prehabilitation program similar to that of Chen J, *et al.*, comparing a control group with a group that underwent prehabilitation strategies for two weeks in patients scheduled to undergo thoracoscopic lobectomy for lung cancer. They reported that there was no statistically significant difference on the "Quality of Recovery 9" questionnaire. They also noted that there were no differences in the incidence and severity of complications 30 days post-surgery between the two study groups. Regarding complications, they concluded that the study had limitations due to the small number of patients, that there could be a risk of false negatives, and that future clinical trials are needed to confirm the effects of prehabilitation.[42,43]

Shen Y *et al.*, in their research on the effects of multimodal and unimodal prehabilitation on postoperative complications in patients undergoing surgery for gastroesophageal cancer, selected clinical trials in which whey protein was administered for at least seven days prior to surgery as a nutritional strategy, along with aerobic exercise, breathing exercises, and/or psychological counseling. For unimodal strategies, only studies involving protein-based nutritional interventions were included. The control groups received no intervention beyond standard care. They found that the rate of postoperative complications was 39. 3 % in the prehabilitation groups and 47. 7 % in the control groups. Groups that implemented multimodal prehabilitation strategies significantly reduced the risk of postoperative complications to 23 %, suggesting that multimodal prehabilitation may reduce the incidence of surgical complications. However, the results of studies in which only unimodal prehabilitation (nutrition) was implemented were not statistically significant.[44]

Recovery time and hospital stay in patients who incorporated whey protein as part of multimodal prehabilitation

The implementation of prehabilitation protocols with a multimodal approach has been associated with a positive impact on postoperative outcomes, as they include nutritional, psychological, and physical therapy strategies for patients undergoing surgery. Díaz-Feijoo *et al.*, conducted a single-center, before-and-after pilot intervention study involving 34 patients with ovarian cancer who were scheduled to undergo cytoreductive surgery; this study incorporated the administration of whey protein into its nutritional strategies. They concluded that the average hospital stay in the intervention group was five days, compared to seven days in the control group.[45]

Chitti W. *et al.*, conducted a randomized clinical trial involving 61 patients with various types of gynecologic cancer to evaluate the effect of whey protein supplementation in the perioperative setting. The results showed that patients who received this supplementation had a hospital stay of 79. 0 ± 16. 7 days, compared to 93. 3 ± 28. 4 days in the control group.[46]

Ahmad *et al.*, evaluated the effects of whey protein supplementation during the postoperative period in 40 patients with mandibular fractures. The patients were divided into two groups. The control group received a personalized diet based on each patient's weight, caloric requirements, and age. The intervention group had whey protein added to their diet. The authors concluded that whey protein supplementation promotes faster recovery of masticatory functions by stimulating bone callus formation and increasing bite force.[47]

Soria *et al.*, conducted a study of 31 patients who had undergone surgery for a femur fracture, who were administered whey protein enriched with leucine and vitamin D for 90 days as part of their postoperative nutritional strategies. They found that these patients experienced a more rapid recovery of functional ability, which led to an earlier return to their daily activities, while maintaining a more adequate nutritional status and better muscle strength.[48]

Minnella E. *et al.*, conducted a clinical trial involving 70 patients scheduled to undergo radical cystectomy. The participants were divided into two groups. The control group received only the standard of care, while the intervention group-referred to as the prehabilitation group-participated in a multimodal program that included, among other measures, whey protein supplementation. The prehabilitation group showed a faster recovery of functional ability and physical fitness compared to the control group. However, the authors did not identify any statistically significant differences in the incidence of complications or in the length of hospital stay.[49]

Ho Y *et al.*, conducted a clinical trial in patients with various types of gynecologic cancer who were scheduled to undergo surgery. The study included 118 patients randomly divided into two groups: the intervention group received a whey protein and carbohydrate load during the preoperative period, in addition to early oral feeding and a solid diet once they could tolerate 500 ml of clear liquids; the control group fasted for 12 hours postoperatively and was allowed to eat once bowel sounds were detected. The researchers concluded from this study that the intervention group showed a significant reduction in the average length of hospital stay compared to the control group ($p < 0.01$), with patients in the intervention group staying up to 21 hours less in the hospital.[50]

Conclusion

Whey protein is a nutritional supplement that has been incorporated into multimodal prehabilitation programs for patients undergoing complex surgeries, yielding positive results such as shorter hospital stays and a faster return to daily activities. One of the limitations of the current evidence is the lack of standardized protocols; in this context, further research is needed to establish evidence-based recommendations regarding dosage, timing of initiation, and optimal duration of supplementation, as well as to identify the clinical characteristics of patients who could derive the greatest benefit from this nutritional intervention.

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