Prehabilitation with Whey Protein Supplementation on Perioperative Functional Exercise Capacity in Patients Undergoing Colorectal Resection for Cancer: A Pilot Double-Blinded Randomized Placebo-Controlled Trial

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ABSTRACT

Background A previous comprehensive prehabilitation program, providing nutrition counseling with whey protein supplementation, exercise, and psychological care, initiated 4 weeks before colorectal surgery for cancer, improved functional capacity before surgery and accelerated functional recovery. Those receiving standard of care deteriorated. The specific role of nutritional prehabilitation alone on functional recovery is unknown.

Objective This study was undertaken to estimate the impact of nutrition counseling with whey protein on preoperative functional walking capacity and recovery in patients undergoing colorectal resection for cancer.

Design We conducted a double-blinded randomized controlled trial at a single university-affiliated tertiary center located in Montreal, Quebec, Canada. Colon cancer patients (n=48) awaiting elective surgery for nonmetastatic disease were randomized to receive either individualized nutrition counseling with whey protein supplementation to meet protein needs or individualized nutrition counseling with a nonnutritive placebo. Counseling and supplementation began 4 weeks before surgery and continued for 4 weeks after surgery.

Main Outcome Measure The primary outcome was change in functional walking capacity as measured with the 6-minute walk test. The distance was recorded at baseline, the day of surgery, and 4 weeks after surgery. A change of 20 m was considered clinically meaningful.

Results The whey group experienced a mean improvement in functional walking capacity before surgery of +20.8 m, with a standard deviation of 42.6 m, and the placebo group improved by +1.2 (65.5) m (P=0.27). Four weeks after surgery, recovery rates were similar between groups (P=0.81).

Conclusion Clinically meaningful improvements in functional walking capacity were achieved before surgery with whey protein supplementation. These pilot results are encouraging and justify larger-scale trials to define the specific role of nutrition prehabilitation on functional recovery after surgery.
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COLORECTAL CANCER IS THE THIRD MOST commonly diagnosed cancer in North America, and it is primarily treated with surgery.[1] Traditionally, surgical "recovery" has been defined by using outcome measures such as length of hospital stay and rates of morbidity; however, these measures are confounded by socioeconomic, cultural, and institutional factors.[2] From a patient's perspective, return to baseline function can mean restoration of activities of daily living, resolution of clinical symptoms, return to work, and improvement in quality of life. A shift from these traditional measures to a more patient-centered outcome measure of recovery, such as function, is required.[2]

The process of enhancing an individual's functional capacity to optimize physiologic reserves before an operation to withstand the stress of surgery has been coined *prehabilitation.*[3,4] A pilot prehabilitation program providing physical exercise, psychological, and nutrition care with whey protein supplementation, initiated 4 weeks before colorectal surgery, produced a mean improvement in walking distance of 40 m, as measured by a 6-minute walk test (6MWT), before surgery and accelerated functional recovery after surgery.[5] Eight weeks postoperatively, 81% of the prehabilitated patients had recovered functional walking capacity, compared with 40% of the control group receiving standard care, independent of traditional outcome measures.[5]

To uncover and target the specific roles of diet and exercise in improving the functional walking capacity of the surgical patient, a similar study was conducted with an exercise-only intervention.[3] One-third of patients deteriorated preoperatively despite participating in an intense exercise regimen, suggesting that exercise alone is insufficient to prepare patients for surgical insult.[3] A limitation of this study was that a nutrition assessment was not conducted. Indeed, exercise is generally accepted to be the main anabolic stimulus, but optimal gains in protein accretion cannot be achieved without adequate substrates.[6] Whey protein substrates have great potential to be used effectively to support postsurgery anabolism. Whey proteins are of high quality,[7] have proved to be effective in modulating postexercise muscle protein synthesis, and are a convenient way to supplement protein needs.[8,9] Whey proteins also have immunomodulating properties,[10] including biosynthesis of antioxidant glutathione,[11] which could attenuate the catabolic effects of surgery and spare protein.

The specific role that nutrition plays in functional capacity before surgery is unclear. Previous studies and systematic reviews evaluating the effect of preoperative nutritional status or nutrition interventions on surgical recovery are limited by the use of traditional measurements of recovery only (eg, length of stay).[12-14] Furthermore, validated functional measures of colorectal surgical recovery have rarely been used in nutrition-focused studies within hospitals currently using enhanced recovery protocols.

The objective of the current study was to provide insight into the role of nutritional prehabilitation on function, a patient-relevant outcome measure of recovery, and more specifically, the role of whey protein supplementation on functional exercise capacity and recovery. A pilot randomized, double-blinded, placebo-controlled trial was conducted in patients undergoing elective resection of colorectal cancer. The study estimated the extent to which a prehabilitation program involving nutrition counseling and whey protein supplementation impacted preoperative functional walking capacity, compared with nutrition counseling alone. The impact was measured by the 6-minute walking test (6MWT), before and after surgery.

MATERIALS AND METHODS

Patients

The study was approved by the McGill University Health Centre Research Ethics Board, Montreal, Quebec, Canada, and the protocol was registered at http://clinicaltrials.gov (NCT 01727570). Consecutive adult patients scheduled for elective resection of nonmetastatic colorectal cancer were approached at their first appointment with their surgeon at a single university-affiliated tertiary center located in Montreal, and written informed consent was obtained in eligible patients. Patients with poor English or French comprehension, milk allergy, or premorbid conditions that contraindicated exercise were deemed ineligible.[5] All patients received standardized perioperative care based on the enhanced recovery after surgery guidelines implemented in the institution in 2010.[15]

Study Design

This study was initially designed as a randomized controlled trial (RCT) with 60 patients; however, reorganizational issues required a change in the original protocol as registered at http://clinicaltrials.gov (NCT 01727570). Due to the lack of personnel to conduct the original postoperative follow-up at 4 and 8 weeks after surgery, patients only received one postoperative follow-up at 4 weeks. Recruitment ended when 48 patients were enrolled. Because of the smaller sample size, fewer follow-up interviews, and decreased power, the original trial became a pilot study to collect supportive data for a future trial with sufficient power, sample size, and staff support.

At the time of consent, patients were instructed by a registered dietitian to complete a 3-day estimated food record of 2 weekdays and 1 weekend day.[16] Participants were required to measure and record the quantity of all foods and beverages consumed, using standard household measures. Approximately 4 weeks before each patient's scheduled operation, medical examinations and nutritional risk screenings were conducted. Baseline questionnaires, biochemical, functional, and anthropometric measurements were also obtained at this time. All measurements were collected again preoperatively (day of surgery) and 4 weeks after the operation by a research assistant who was blinded to group assignment. Patients were randomly assigned on a 1:1 ratio by computer-generated random numbers to receive either individualized nutrition counseling with whey protein supplementation or individualized nutrition counseling with placebo supplementation. No group stratifications were performed. Group allocation was concealed by using sequentially numbered sealed envelopes. The scheduling of surgery was not affected by study group.

Compliance was measured by using a diary to document the quantity of the nutritional supplement taken each day. Patients were contacted weekly by the research assistant and queried with a standardized set of open-ended questions designed to identify problems with compliance to the supplement regimen.

Nutrition Intervention

Both study groups participated in identical nutrition assessment and counseling sessions (90 minutes total) provided by a registered dietitian at their baseline appointment. During this session, each patient was provided with a personalized nutrition care plan based on their dietary needs as determined through analysis of food records and estimated requirements.

Dietary protein and energy intake were estimated from the food records provided by using food exchange lists and a food composition database.[17] Dietary intake was then evaluated based on individually calculated energy and protein requirements (determined using indirect calorimetry), and food choices were compared with *Eating Well with Canada's Food Guide* recommendations.[18]

Individualized nutrition care plans focused on meeting energy and protein requirements with appropriate food choices, management of cancer-related symptoms (such as diarrhea and constipation), blood glucose control, optimization of body composition (ie, weight loss or gain if necessary), and nutrient intake by using practical suggestions based on actual intake.

Both groups received a daily supplement regimen. The placebo group received a standard amount of a nonnutritive product composed of a sweetener (Crystal Light, Kraft Foods) for palatability and Resource Thicken Up (Nestlé Nutrition) (ingredients: modified cornstarch). Patients were blinded to the type of supplement by administering the sachets unlabeled. Regardless of the group assignment, patients were instructed to take the supplement once per day (placebo or whey) for approximately 4 weeks leading up to their surgery and the first 4 weeks after surgery.

A whey protein supplement (Immunocal, Immunotec Inc) was provided to the whey protein group in a quantity that matched the patient's need according to the estimated deficit in dietary protein intake. This deficit was determined based on the difference between usual protein intake obtained from the food record, and calculated protein requirement. Individual protein needs were calculated as 20% of total energy expenditure (approximately 1.2 to 1.5 g protein/kg/d), determined by using indirect calorimetry, conforming with the guidelines for surgical patients set by the European Society for Clinical Nutrition Metabolism (ESPEN).[19] The whey protein group was asked to take the supplement with a nonnutritive sweetener (Crystal Light) for palatability.

Measurements

The primary outcome was functional walking capacity, as measured with the 6MWT preoperatively (day of surgery) and 4 weeks after surgery. The 6MWT, which has been validated in the colorectal surgical population, evaluates the ability of an individual to maintain a moderate level of aerobic endurance and reflects capacity to perform activities of daily living.[20,21] For instance, a 6MWT score greater than 432 m is needed to provide the stamina to cross four lanes of traffic while the green light is flashing.[3] Instructions were provided to participants as previously described.[5,22] In our original protocol, we established that change in 6MWT of 20 m would be considered meaningful, because this is the estimated measurement error in community-dwelling elderly people.[23] A recent study in colorectal surgery supported the clinical meaningfulness of this change by using anchor-based methods (minimal clinically important difference estimated at 14 m for longitudinal comparisons and 19 m for between-group comparisons).[24] Age- and sex-specific predicted distances were calculated by using the following formula:

$$\text{Predicted distance walked in 6 min (m)}$$

$$868 - (\text{age} \times 2.9) - (\text{female} \times 74.7)$$

where age is in years, and the value "1" is assigned for females.[5,25]

Secondary outcomes included self-reported physical activity and health-related quality of life. Self-reported physical activity was measured by the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire, which is a validated measure of recovery after elective abdominal surgery.[26] Patients estimate the number of total hours spent performing 41 listed activities of various intensities during the previous week. Weekly energy expenditure (kcal/kg/wk) was estimated by adding the energy cost of each of the activities performed (metabolic equivalents) over the week.[26]

General health-related quality of life was measured using the 36-Item Short Form Health Survey (SF-36), which is commonly used in surgical populations. This questionnaire includes eight subscales: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health; each subscale is scored on a 0 to 100 scale. Two summary scores can be derived: the physical component summary and mental component summary scores.[27-29]

Resting energy expenditure was measured at the baseline assessment by using indirect calorimetry to determine individualized total energy needs (Sensormedic Vmax 229 Metabolic Cart System). Patients were instructed to lie in a semi-recumbent position, breathing room air in a ventilated hood for 20 minutes, while oxygen consumption and carbon dioxide production were measured. Total energy expenditure was determined individually by using a stress factor of 1.3 for major surgery and an appropriate activity factor.[30]

The patient-generated subjective global assessment (PG-SGA) is a validated nutritional assessment tool for cancer patients. It was used at baseline to globally classify patients as (A) well nourished, (B) moderate or suspected undernutrition, and (C) severely undernourished, based on weight loss, functional limitations, dietary intake, and presence of symptoms that affect intake.[31-33] The Nutrition Risk Screening tool—2002 (NRS-2002) was also used at baseline because it is presently regarded as the screening tool that best predicts postsurgical complications, and its use is recommended by recent consensus guidelines from the North American Surgical Nutrition Summit for surgical patients.[34,35] Body composition was measured by using a hand-to-foot bioelectrical impedance analysis (Biospace Inbody 320).[36]

Biological indices measured included albumin, C-reactive protein (CRP), and glycosylated hemoglobin (HbA1c). Plasma HbA1c was measured by high-performance liquid chromatography by using the Somagen Tosoh G8 and was used as a marker of glucose control for nutrition assessment and care plans. Glasgow Prognostic Score was calculated to reflect surgical risk associated with abnormalities in CRP or albumin concentration before surgery.[37] A score of 2 is given if both blood abnormalities are present, and a score of 1 is given if only one value is abnormal, whereas a score of 0 is given if neither value is abnormal.[37] Serum CRP was measured by rate turbidimetry by using a Beckman Coulter, and serum albumin was measured with a synchron LX system (Beckman Instruments).

Postoperative complication rates were graded by severity by using the Dindo-Clavien classification, in which grade I complications require bedside management; grade II complications require pharmacologic treatment; grade III complications require surgical, endoscopic, or radiologic

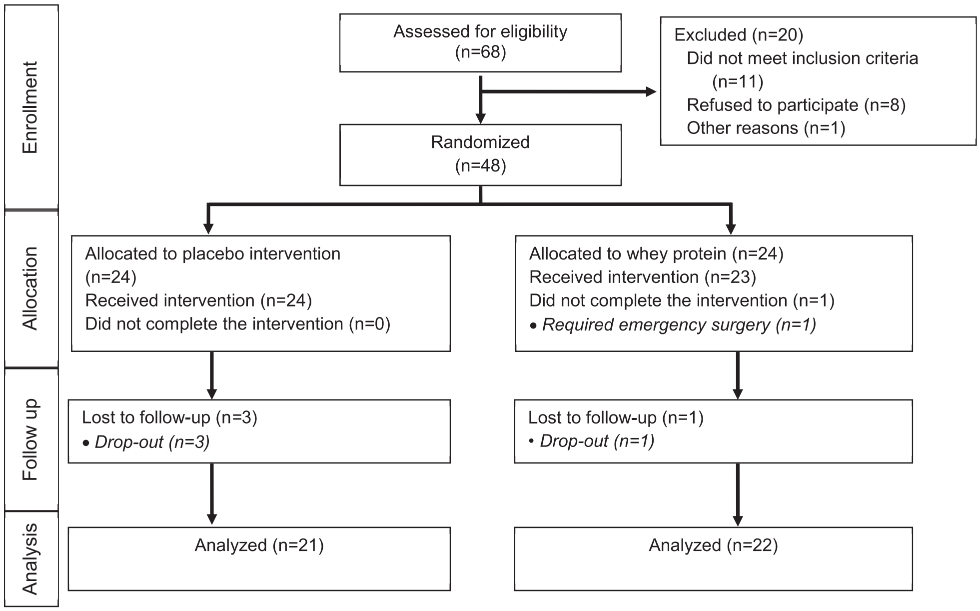

Figure. Assessment, randomization, and end-of-study status for colorectal cancer patients in a whey protein supplement or placebo program.

intervention; and grade IV complications require intensive care treatment.[38]

Statistical Analysis

All randomized patients were analyzed in their assigned treatment group regardless of compliance. A complete case analysis without imputation of missing values was conducted given the low rate of missing data (less than 10%) for our primary preoperative outcome. All analyses were performed with Stata 12 (2011, StataCorp). Normality of data distribution was verified visually by using histograms. Changes in 6MWT and other variables over the preoperative period (day of surgery-baseline values) were calculated and compared between groups. Continuous data with normal distribution were reported as mean±standard deviation (SD) and compared using independent Student's *t* test. Continuous data with non-normal distribution were reported as median (interquartile range) and compared by using a Wilcoxon rank-sum test. Categorical variables were reported as frequency (%) and compared using Fisher's exact test. Ranges of values and 95% confidence intervals (95% CI) were provided for relevant variables. A *P* value <0.05 was considered statistically significant.

RESULTS

Patients

A total of 68 patients were approached for consent, of which 48 patients were randomized (Figure) between September 2012 and October 2013. Four patients dropped out (ie, did not complete any follow-up assessment), and one patient underwent emergency surgery after randomization. Therefore, a total of 43 patients were analyzed (22 in the whey protein group and 21 in the placebo group). Patient clinical characteristics (Table 1) and baseline measures (Table 2) were similar between groups. The median duration between the baseline assessment and surgery was 24.5 (14.5 to 37) days for the placebo and 33.5 (22.5 to 48.5) days for the whey protein group.

Outcomes

Nutrition Prescription and Compliance to the Program. The mean (SD) for the whey protein supplement prescription was 19.8 (7.8) g. Compliance to the prescription was 96.6% (95% CI: 91% to 100%) for the placebo group and 93.7% (95% CI: 86% to 100%) for the whey protein group (P=0.51).

Functional Measurements. Data for 6MWT were missing for four patients preoperatively (n=2 placebo, n=2 whey group) and 12 patients postoperatively (n=4 placebo, n=8 whey group). The mean (SD) in the placebo group improved while waiting for surgery by +1.2 m (65.6; range=−202 to 147 m), whereas the whey group experienced a clinically meaningful improvement of +20.8 m (42.6; range=−40 to 112 m) (Tables 3 and 4): a mean difference between the 2 groups of 19.6 m (95% CI=-6.627 to 29.13, P = 0.27). This suggests that patients supplemented with whey protein were able to walk further in 6 minutes at the time of surgery than at baseline. In fact, 50% of the whey protein group improved beyond their baseline function (>20 m), whereas only 30% of the placebo group improved (P=0.63). Four weeks after surgery (Table 5), recovery rates were similar between groups: the mean (SD) 6MWT was found to be 424.7 (89.8) m and 425 (146.0) m for the placebo and whey groups, respectively (P=0.83).

Self-Reported Outcomes. Data were missing for at least one of the secondary outcomes in nine patients (n=5 placebo, n=4 whey group) for the preoperative period and for 13 patients for the postoperative period (n=4 placebo, n=9 whey protein) because of loss in follow up (Tables 3 and 5).

Table 1. Demographic and clinical characteristics for 43 colorectal cancer patients in a whey protein supplement or placebo program

Demographic and clinical information	Placebo (n=21)	Whey protein supplementation (n=22)	*P* value
	←mean±standard deviation→		
Age, y	69.1±9.4	67.6±11.5	0.64
	←*n* (%)→		
Male sex	15 (71)	13 (59)	0.52
American Society of Anesthesiologists physical status[a]			0.11
I	0 (0)	2 (11)	
II	13 (65)	7 (38)	
III	7 (35)	9 (50)	
Type II diabetes	1 (4)	4 (19)	0.34
Tumor-node-metastasis cancer stage[b]			0.54
0	2 (13)	4 (20)	
1-2	6 (40)	10 (50)	
3	7 (47)	6 (30)	
Neoadjuvant therapy[c]	5 (24)	5 (23)	>0.999
Laparoscopic procedure[d]	15 (75)	18 (90)	0.40
Type of resection			>0.999
Colon[e]	9 (45)	9 (50)	
Rectum[f]	11 (55)	9 (50)	
New stoma[g]	4 (2)	7 (39)	0.29

[a]American Society of Anesthesiologists physical status is a classification system used to assess the degree of a patient's preoperative physical state before induction. Higher values represent greater deconditioning.
[b]Cancer is staged from 0 to IV. Higher values represent more advanced cancer.
[c]Neoadjuvant therapy refers to chemotherapy or radiation therapy.
[d]Laparoscopic refers to a minimally invasive surgery rather than open surgery.
[e]Includes right- and left-hemicolectomy and sigmoid resection.
[f]Includes anterior resection, low anterior resection, and abdominoperineal resection.
[g]Stoma refers to a surgical opening for a colostomy or ileostomy.

Preoperative SF-36 and CHAMPS scores were consistent with those observed in previous studies involving similar surgical populations.[5,39] No statistically significant between-group median differences in self-reported physical activity were seen during the preoperative period (placebo group median=0; range=−678.8 to 39.9 vs whey protein group median=0; range=−161.1 to 168.0). Likewise, no between-group differences in changes were found in the Mental Component Summary Score (placebo group median=+2.3; range=−15.7 to 14.5 vs whey protein group median=−1.2; range=−10.1 to 25.2) or Physical Component Summary Score of the SF-36 (placebo group median=+0.1; range=−20.5 to 13.9 vs whey protein group median=+1.1, range=−16.9 to 40.8). At 4 weeks after surgery, CHAMPS and SF-36 scores were not statistically different between groups (Table 5).

Perioperative Outcomes. No differences were seen in the incidence of overall 30-day complications, complication severity, or emergency department visits and readmission, as well as no difference in median length of stay (Table 5).

DISCUSSION

The results of this pilot study provide insight into the role of nutrition prehabilitation on functional capacity. Preoperative nutrition counseling with whey protein supplementation produced a clinically meaningful increase >20 m in functional walking capacity before surgery. Although the results are promising and warrant further larger-scale investigation, practical clinical inferences cannot be made because of the small sample size, variability, and pilot nature of the study.

Gastrointestinal cancers often create unique barriers to nutritional adequacy, such as an intestinal obstruction that impairs absorption and restricts dietary choices. In fact, a retrospective chart review showed that 28% of colorectal cancer patients complained of pain, loss of

Table 2. Baseline nutritional, functional, and self-reported physical activity measures for 43 colorectal cancer patients in a whey protein supplement or placebo program

Nutritional and functional status at baseline	Placebo (n=21)	Whey protein supplementation (n=22)	*P* value
Body mass index,[a] mean±SD[b]	25.2±4.5	26.6±5.0	0.37
Percent lean body mass, mean±SD	73±9	69±7	0.21
Percent fat body mass, mean±SD	35±10	40±12	0.21
Resting energy expenditure, mean±SD	1,261.7±170.6	1,286.5±255	0.73
Albumin (g/dL), mean±SD	4.07±0.4	3.9±0.4	0.30
C-reactive protein (mg/dL), median [interquartile range (IQR)]	2.4 [1.2-4.5]	3 [1.5-6.7]	0.37
Hemoglobin A1c (%), median [IQR]	5.6 [5.4-6.0]	6.0 [5.6-6.8]	0.08
Glasgow prognostic score,[c] n (%)			0.30
0	19 (95)	16 (76)	
1	0 (0)	3 (14)	
2	1 (5)	2 (10)	
Patient-generated subjective global assessment,[d] n (%)			>0.999
A, well-nourished	14 (67)	13 (59)	
B, moderate or suspected malnutrition	6 (28)	7 (32)	
C, severely malnourished	1 (5%)	2 (9%)	
Nutrition risk screening 2002,[e] n (%)			0.57
1-2	7 (33)	7 (31)	
3-4	13 (62)	14 (64)	
5-6	1 (4)	1 (4)	
6MWT (m),[f] mean±SD	440.9±89.5	423.6±132.5	0.62
Percent predicted 6MWT,[fg] mean±SD	67.2±13.5	63.2±17.9	0.42
Self-reported physical activity (CHAMPS)[h] (kcal/kg/week), median [IQR]	23.6 [2.6-105]	32.4 [11.8-58.4]	0.73
Physical component summary score (SF-36),[i] median [IQR]	50.6 [36.3-52.7]	44.1 [41.5-56.5]	0.04
Mental component summary score (SF-36),[i] median [IQR]	49.5 [44.6-57.8]	42.8 [34.7-52.6]	0.15
Grip strength left hand (kg), mean±SD	30.2±8.8	30.6±10.7	0.90
Grip strength right hand (kg), mean±SD	30.2±8.4	30.5±11.1	0.92

[a]Calculated as kg/m^2.
[b]SD=standard deviation.
[c]Glasgow Prognostic Score reflects surgical risk associated with abnormalities in C-reactive protein or albumin concentration before surgery. Higher values represent greater abnormalities and therefore risk.
[d]Patient-generated subjective global assessment is a nutritional assessment tool for cancer patients.
[e]Nutrition risk screening 2002 is a nutrition risk screening tool used for surgical patients. A score >3 indicates that the patient is nutritionally at risk, and the need for a nutritional care plan should be assessed.
[f]6MWT=6-minute walk test.
[g]Percent predicted 6MWT is the calculated predicted distance walked in 6 minutes based on age and sex.
[h]CHAMPS=community healthy activities model program for seniors.
[i]SF-36=36-item short form health survey. Physical and mental component summary scores are standardized to a mean of 50 and standard deviation of 10.

appetite, and diarrhea on their first visit to their surgeon.[40] Likewise, one in five colorectal cancer outpatients are reported to be malnourished, with more than half of these patients experiencing weight loss before surgery.[41] Comparably, approximately one-third of the currently studied patients were found to be at nutritional risk by using the PG-SGA nutritional assessment tool. However, approximately 60% of our patients scored a 3 to 4 when screened with the NRS-2002 tool, indicating the need for further nutritional assessment and possible intervention.

Table 3. Changes in 6-minute walk distance, self-reported physical activity, physical function, and grip strength for 43 colorectal cancer patients in a whey protein supplement or placebo program before surgery compared with baseline

Preoperative change	Placebo (n=21)	Whey protein supplementation (n=22)	*P* value
Change in 6MWT[a] distance (m), mean±standard deviation (SD)	+1.2±65.5	+20.8±42.6	0.27
Change in self-reported physical activity (CHAMPS)[b] (kcal/kg/wk), median [interquartile range (IQR)]	0 [−17.3 to +8.4]	0 [−10.5 to +15.4]	0.34
Change in physical component summary (SF-36)[c], median [IQR]	+0.1 [−5.1 to +3.1]	+1.1 [−0.6 to +5.7]	0.46
Change in Mental Component Summary (SF-36)[c], median [IQR]	+2.3 [−1.3 to +6.0]	-1.2 [−3.8 to +4.3]	0.31
Change in grip strength left hand (kg), mean±SD	+0.65±3.0	+0.18±3.2	0.63
Change in grip strength right hand (kg), mean±SD	+0.52±3.7	−0.44±3.0	0.37

[a]6MWT=6-minute walk test.
[b]CHAMPS=community healthy activities model program for seniors.
[c]SF-36=36-item short form health.

Nutrition counseling with whey protein supplementation produced a particularly intriguing and clinically relevant mean improvement of +20.8 (42.6) m in functional walking distance before surgery. These results are very similar to a recent RCT[39] in which an improvement of +25.2 m (50.2) was found when a *trimodal* prehabilitation program was initiated 4 weeks before surgery. Indeed, the mean preoperative gain of functional walking distance in the whey protein group was +37.2 m greater than that of a group receiving standard of care preoperatively from a previous prehabilitation trial (+20.8±42.6 vs −16±46).[39] This difference is greater than the 20-m change in walking capacity required to be considered clinically important.[3,24] The observed improvement may be the result of identifying and correcting barriers to inadequate intake that may contribute to a loss of physiologic reserve before surgical insult. Inadequate protein intake is associated with loss of lean mass, which can impair physiologic function.[42] In contrast, provision of protein, regardless of whether energy requirements are met, can maintain lean mass and reduce the risk of incident frailty in older adults.[43] Recent

Table 4. Forty-three colorectal cancer patients in a whey protein supplement or placebo program exhibiting clinically important changes in the 6-minute walk distance over the preoperative period and postoperative period

	Placebo (n=21)	Whey protein supplementation (n=22)	*P* value
	←——*n (%)*	——→	
Preoperative change[a]			
Deterioration[b]	4 (21)	3 (15)	0.633
No change[c]	9 (47)	7 (35)	
Improvement[d]	6 (31)	10 (50)	
Postoperative change[e]			
Deterioration[b]	9 (52)	6 (42)	0.81
No change[c]	4 (23)	4 (28)	
Improvement[d]	4 (23)	4 (28)	

[a]Difference between baseline and immediately presurgery assessments.
[b]Greater than 20 m *decrease* compared with baseline.
[c]Within 20 m of baseline.
[d]Greater than 20 m *increase* compared with baseline.
[e]Difference between baseline and 4-weeks-after-surgery assessments.

Table 5. Clinical, functional, and self-reported physical activity outcomes for 43 colorectal cancer patients in a whey protein supplement or placebo program 4 weeks after surgery

Postoperative outcomes	Placebo (n=21)	Whey protein supplementation (n=22)	*P* value
Patients with at least 1 complication within 30 days of surgery, n (%)	9 (42)	8 (38)	0.75
Ileus	7 (33)	7 (33)	
Wound dehiscence	0	1 (4)	
Abscess	1 (4)	2 (9)	
Urinary retention	1 (4)	0	
Urinary tract infection	0	2 (9)	
Pneumonia	1 (4)	0	
Pleural effusion	1 (4)	0	
Grade of most severe complication,[a] n (%)			0.88
Grade I	6 (28)	4 (19)	
Grade II	2 (9)	1 (4)	
Grade III	1 (4)	2 (9)	
Grade IV	1 (4)	0	
30-day readmission, n (%)	5 (23)	2 (9)	0.41
Days in the hospital, median [interquartile range (IQR)]	4 [3-10]	5 [3-13]	0.78
6MWT[b] (m), mean±standard deviation (SD)	424.7±89.8	425±146.0	0.83
Percent change in lean body mass compared with baseline, mean±SD	−1.8±2.9	−0.3±7.1	0.43
Percent change in fat compared with baseline, mean±SD	0.8±4.3	−0.7±8.5	0.50
Self-reported physical activity (CHAMPS)[c] (kcal/kg/wk), median [IQR]	15.2 [3.6-34.1]	10.5 [5.7-26.2]	0.91
Physical component summary score (SF-36),[d] median [IQR]	36.5 [34.5-42.8]	41.3 [34.2-46.5]	0.76
Mental component summary score (SF-36)[d], median [IQR]	41.3 [35.6-55.8]	47.7 [38.1-53.8]	0.73
Grip strength left hand (kg), mean±SD	30.1±8.9	29.1±11.7	0.79
Grip strength right hand (kg), mean±SD	30.5±8.8	30.7±10.9	0.83

[a]Dindo-Clavien classification was used to grade postoperative complication rates. Higher scores represent greater severity of complications.
[b]6MWT=6-minute walk test.
[c]CHAMPS=community healthy activities model program for seniors.
[d]SF-36=36-item short form health. Physical and mental component summary scores are standardized to a mean of 50 and standard deviation of 10.

consensus recommendations from the North American Surgical Nutrition Summit suggest a shift from focusing on postoperative nutrition to preventive preoperative nutrition therapy. The consensus emphasized the concept of preoperative "metabolic preparation" in all patients deemed to be at nutritional risk.[34]

Considering the impact of cancer on nutritional status[44] and the effect of malnutrition on surgical outcome,[19,45] it is logical that a nutrition regimen intended to optimize nutritional intake (including protein provision to maintain lean body mass and skeletal muscle function[46,47]) would prepare patients for surgery.[48,49] An earlier RCT in patients undergoing elective colorectal surgery comparing home-based programs of moderate vs intense exercise without psychological or nutritional care highlights the important role of nutrition: while waiting for surgery, functional walking capacity deteriorated in one-third of patients assigned to the intense exercise program.[3] This finding is supported by a recent systematic review of eight RCTs in which physical exercise alone was not found to improve clinical outcomes in the context of major surgery.[50] Moreover, exercise stimulates anabolic signaling, and feeding augments this effect.[6] In fact, exercise alone, in the absence of adequate nutrition, will not lead to maximal muscle protein accretion,[51-53] and, as recent evidence suggests, will not produce maximal improvements in functional capacity.[3]

Despite the whey protein group's mean improvement in preoperative functional walking capacity, recovery rates 4 weeks after surgery were similar between groups: 46% of the placebo group and 56% of the whey group had returned to within 20 m of their baseline values (P=0.81). A 20-m change in 6-minute walking distance has been used in previous trials as a threshold of recovery,[3,5] and a recent study in colorectal surgery supported the clinical meaningfulness of this change by using anchor-based methods.[24] Discerning whether recovery rates would have continued to be similar between groups 8 weeks after surgery or whether the recovery rates would have been similar to previous trials at this time point is difficult. Indeed, the trajectory of recovery, as reported in previous prehabilitation trials,[5,39] indicates that most patients after prehabilitation do not recover functional walking distance 4 weeks after surgery, but do return to baseline values by the 8th postoperative week.

Furthermore, recovery of functional capacity during the first 4 weeks after surgery might have been influenced by an insufficient dietary protein intake after surgery to compensate for catabolic demands. A recent observational trial identified that in the immediate postoperative period colorectal surgical patients do not meet dietary protein requirements.[54] With this in mind, whey protein supplementation might need to be provided in a greater quantity after surgery to offset a drop in dietary protein intake in order to achieve maximal anabolic gains. That being said, whey protein supplementation did support a mean recovery in functional walking distance at 4 weeks after surgery of +69 m more than a standard of care group from a previous trial (ie, 425±146 m vs 356±71 m).[5] This suggests that nutrition prehabilitation might play a role in preoperative care and postoperative recovery.

Finally, not only was nutrition prehabilitation implemented successfully in the preoperative period, but the regimen was also acceptable to patients, as evidenced by the high compliance to the nutrition prescription provided. The mean (SD) intake of whey protein was 19.8 (7.8) g per day (provided to bring dietary protein intake up to assessed needs). Mean compliance to the supplementation was found to be 93.7%, and mean compliance to our previous trimodal intervention was found to be 78%.[39]

The study has limitations. In light of the small sample size and missing postoperative data, further larger studies are required to determine whether the observed improvement with whey protein supplementation is statistically significant and to verify whether the preoperative change found in functional capacity is sufficient to restore recovery after surgery. The high inter-subject variability observed for the 6MWT could be the result of grouping well-nourished with undernourished or frail patients. Although investigating how a subset of undernourished or frail patients responded to the intervention would have been interesting, the sample size was too small for regression analysis. Furthermore, compliance of supplement intake was assessed; however, compliance to dietary suggestions was not measured before surgery. This information would have been useful to determine whether the diets were essentially isonitrogenous, so that the differences observed could be related to the supplement alone. We chose to supplement protein in a quantity that would meet dietary needs. Recent evidence suggests that elderly patients require protein in 30-g doses to counteract the anabolic resistance of aging.[55] Future studies might provide additional protein to this subgroup.

CONCLUSION

This pilot study suggested that nutrition played an integral role in preparing patients for surgery. The results are encouraging and justify larger-scale trials to define the specific role of nutritional prehabilitation on functional recovery after surgery.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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