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Randomized Control Trials

Trimodal prehabilitation for colorectal surgery attenuates post-surgical losses in lean body mass: A pooled analysis of randomized controlled trials

Chelsia Gillis [a, *], Tanis R. Fenton [b], Tolulope T. Sajobi [c], Enrico Maria Minnella [d], Rashami Awasthi [d], Sarah-Ève Loiselle [e], A Sender Liberman [f], Barry Stein [f], Patrick Charlebois [f], Francesco Carli [d]

[a] *Cumming School of Medicine, Department of Community Health Sciences, University of Calgary, AB, Canada*
[b] *Community Health Sciences, Institute of Public Health, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, and Nutrition Services, Alberta Health Services, AB, Canada*
[c] *Cumming School of Medicine, Department of Community Health Sciences & O'Brien Institute for Public Health, University of Calgary, Calgary, Canada*
[d] *Department of Anesthesia, McGill University, Montreal, QC, Canada*
[e] *Department of Nutrition and Food Services, McGill University, Montreal, QC, Canada*
[f] *Department of Surgery, McGill University, Montreal, QC, Canada*

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SUMMARY

Background & aims: Preservation of lean body mass is an important cancer care objective. The capacity for prehabilitation interventions to modulate the lean body mass (LBM) of colorectal cancer patients before and after surgery is unknown.
Methods: A pooled analysis of two randomized controlled trials of trimodal prehabilitation vs. trimodal rehabilitation at a single university-affiliated tertiary center employing Enhanced Recovery After Surgery (ERAS) care was conducted. The prehabilitation interventions included exercise, nutrition, and anxiety-reduction elements that began approximately four weeks before surgery and continued for eight weeks after surgery. The rehabilitation interventions were identical to the prehabilitation interventions but were initiated only after surgery. Body composition, measured using multifrequency bioelectrical impedance analysis, was recorded at baseline, pre-surgery, 4 and 8 weeks after surgery. The primary outcome was change in LBM before and after colorectal surgery for cancer. A mixed effects regression model was used to estimate changes in body mass and body composition over time controlling for age, sex, baseline body mass index (BMI), baseline six-minute walk test (6MWT), and postoperative compliance to the interventions. NCT02586701 & NCT01356264.
Results: Pooled data included 76 patients who followed prehabilitation and 63 patients who followed rehabilitation ($n = 139$). Neither group experienced changes in preoperative LBM. Compared to rehabilitated patients, prehabilitated patients had significantly more absolute and relative LBM at four and eight-weeks post-surgery in models controlling for age, sex, baseline BMI, baseline 6MWT, and compliance to the postoperative intervention.
Conclusion: Trimodal prehabilitation attenuated the post-surgical LBM loss compared to the loss observed in patients who received the rehabilitation intervention. Patients who receive neither intervention (i.e., standard of care) would be likely to lose more LBM. Offering a prehabilitation program to colorectal cancer patients awaiting resection is a useful strategy to mitigate the impact of the surgical stress response on lean tissue in an ERAS setting, and, in turn, might have a positive impact on the cancer care course.
Clinical trial registration: NCT02586701 & NCT01356264 (clinicaltrials.gov).

* Corresponding author. Cumming School of Medicine, Department of Community Health Sciences, University of Calgary, TRW Building, 3rd Floor, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada.
E-mail address: chelsia.gillis@ucalgary.ca (C. Gillis).

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1. Introduction

Colorectal cancer is one of the most commonly diagnosed cancers in North America [1]. Resection of the primary tumor is the mainstay of treatment; however, the surgery itself is often only one element of the patients' cancer care course. As a result, the colorectal cancer patient bears compounding metabolic demands requiring regular attention to the optimization of modifiable risk factors throughout the cancer care journey to realize the best health outcomes [2].

Surgical prehabilitation employs multimodal interventions in the pre-surgery period to prepare patients emotionally and physically to withstand the immediate and long-term impacts of surgery [2,3]; similarly, to the way an athlete would prepare for the stressors of an upcoming competition. The objective is to fortify functional reserve prior to surgery, thereby reducing treatment-related morbidity and promoting an earlier return to pre-surgery physical functioning [4,5]. Three randomized controlled trials (RCTs) provide evidence that multimodal prehabilitation successfully alters the typical trajectory of functional recovery (i.e., return to pre-surgery function, as defined by the six-minute walk test) for patients undergoing elective major abdominal operations [6–8] and reduces postoperative complications [6].

Much of the work concerning prehabilitation to date has focused on clinical and functional surgical recovery with little attention to the impact of prehabilitation on lean body mass (LBM). Body composition parameters, such as the presence of obesity or muscle depletion, have been reported to influence surgical and oncological outcomes in patients with colorectal cancer [9–11]. Likewise, conservation of LBM is increasingly recognized as an important cancer care objective [9,12]. The capacity for prehabilitation to modulate the LBM of colorectal cancer patients before and after surgery has not, to our knowledge, been studied previously.

2. Materials & methods

Original data from two of our groups' previously published prehabilitation vs. rehabilitation trials were pooled [7,8] to provide adequate power to detect a significant difference in LBM changes between groups. In brief, for both studies, adults scheduled for colorectal resection of localized disease were selected for study at a single university-affiliated tertiary care center located in Montreal, Canada, and enrolled after informed consent was given. Subjects were not eligible if they did not speak English or French or if they had premorbid conditions that contraindicated exercise. All patients received perioperative care guided by Enhanced Recovery After Surgery (ERAS) [13–15] and the scheduling of surgery was not affected by study group.

Approximately 4 weeks before each patient's scheduled operation, a baseline assessment and study measurements were completed. All measurements were recorded at baseline, pre-surgery, four and eight weeks after surgery. Upon completion of the baseline assessment, patients were randomly assigned, on a 1:1 ratio by computer generated random numbers, to their treatment group. Both trials involved concealed randomization in sealed envelopes to a trimodal prehabilitation arm or a trimodal rehabilitation arm.

2.1. Trimodal prehabilitation interventions

The trimodal prehabilitation interventions of both studies included exercise, nutrition, and anxiety-reduction components that *began approximately four weeks before surgery and continued for eight weeks after surgery*. Each patient received a baseline appointment with a kinesiologist, dietitian, and an expert trained in psychology – all of whom assessed the patient and provided personalized instructions.

Both studies included an identical nutrition and psychological intervention. The nutrition component involved personalized dietary counseling and whey protein supplementation (Immunocal, Immunotec Inc) to achieve a minimum daily dietary intake of 1.2 g protein/kg of ideal body weight. In addition, the personalized nutrition care plans focused on managing cancer-related symptoms (such as diarrhea and constipation), blood glucose control, optimization of body composition (i.e., weight loss or gain if necessary), and optimizing nutrient intake by using practical suggestions based on actual intake. The anxiety-reduction components involved deep breathing instructions and personalized relaxation exercises to be performed at home a minimum of twice per week.

The exercise components differed slightly between the two studies: one study employed a home-based exercise regimen [7] and the other study employed a home-based regimen with an additional supervised group exercise session once per week [8]. The home-based exercise regimen involved a prescription of unsupervised total-body exercise of up to 50 min for at least 3 days per week, alternating between aerobic and resistance training [7]. The weekly supervised exercise session was structured similarly to the home-based regimen but was provided under the supervision of the kinesiologist in the hospital once per week before surgery [8]. Patients in the latter study were also encouraged to resume exercises during hospitalization once cleared for mobilization by nursing staff. Prehabilitated patients in both studies continued the home-based exercise regimen, whey protein supplementation, and relaxation exercises for 8 weeks after surgery.

2.2. Trimodal rehabilitation interventions

In both studies, the rehabilitation interventions were structured identically to the trimodal prehabilitation intervention with home-based exercise [7,8]. A few days before the scheduled operation, the patients randomized to the rehabilitation control group received a preoperative appointment that was identical to the prehabilitation group, including the personalized assessment and trimodal prehabilitation instructions. Although both studies [7,8] required that patients commence the rehabilitation interventions only after surgery and continue the intervention for 8 weeks postoperatively, one study [8] additionally encouraged patients to exercise during hospitalization once cleared for mobilization by nursing staff.

2.3. Measurements

2.3.1. Body composition

The primary outcome was change in LBM before and after colorectal surgery for cancer. Measurement of body composition was accomplished using a multi-frequency bioelectrical impedance analysis (BIA) (BioSpace InBody 320). This device uses eight points of tactile electrodes (contact at the hands and feet), enabling segmental impedance measurements of the right arm, left arm, trunk, right leg, left leg. The InBody 320 correlates well with Dual-energy X-ray absorptiometry (DXA) measurements (the preferred method for measuring body composition) in the general population (aged >60 years, $r = 0.83–0.97$ for males and females) [16] and when compared with several other BIA methods, the InBody demonstrated the least estimation error [17]. Moreover, BIA was recently validated for use in the colorectal cancer population: fat-free mass estimates showed excellent agreement with DXA ($r = 0.98$ for segmental BIA using eight tactile electrodes and the manufacture's equations) [18]. All our measurements were performed following standardized procedures according to the manufacturer: patients standing barefoot on the scale, after emptying of the bladder, and with heavy clothing and metal objects removed. The manufacturer's proprietary equations were used to estimate body fat mass (FM) and LBM, which were recorded in absolute terms (kg), and relative to body mass (%).

2.3.2. Six-minute walk test (6MWT)

Functional recovery, an important patient-centered outcome [19,20], was evaluated using the six-minute walk test (6MWT) [21]. The 6MWT evaluates walking endurance capacity and is a valid measure of functional recovery post-colorectal surgery [21,22]. A pooled analysis of these findings has been published elsewhere [23].

2.3.3. Intervention compliance

All patients were given a booklet containing personalized intervention instructions and a diary to record completed exercise and relaxation activities as well as the whey protein supplements consumed. Compliance to the intervention prescription was calculated on a weekly basis for each participant (as a percentage based on self-reported data). The compliance value was an equally weighted average among all three interventions based on how closely the patients' self-reported activities matched their personalized prescriptions. To reinforce compliance to the program, patients were contacted on a weekly basis by telephone and asked a standardized set of open-ended questions.

2.4. Statistical analysis

Based on an RCT in colorectal surgery patients who received nutrition prehabilitation vs. placebo [24], the difference in total lean mass lost at 4 weeks after surgery between groups was 1.5 kg. We estimated that 60 patients per group would be required to achieve a 1.5 kg difference (assuming 3 kg standard deviation) in lean mass with a power of 80% and an α-error of 0.05.

Raw data from two RCTs [7,8] of prehabilitation vs. rehabilitation for colorectal cancer surgery were pooled: data from the prehabilitation arms were pooled, while the data from the rehabilitation arms were pooled. The pooled dataset included only the patients with a baseline LBM measure. To ensure the data could be pooled, functional and anthropometric outcomes of the two studies were stratified to permit comparisons. Outcome differences between the two studies were tested using *t*-test and considered significant if $P < 0.05$. Univariate and multiple regression analyses were also conducted to assess whether either study acted as an independent predictor of LBM recovery (8 weeks after surgery − baseline), which would have indicated that these studies produced different findings for LBM and should not be pooled. The multiple regression model included age, BMI, and baseline 6MWT as continuous variables, and sex (female as reference value) and study (trimodal home-based prehabilitation program [7] as the reference value vs. trimodal home-based prehabilitation program with a weekly supervised session [8]) as dichotomous variables.

Unadjusted mean absolute and relative changes in LBM and FM at each time point were evaluated with a paired t-test. Given that these randomized trials were pooled, randomization may not uphold; a mixed effects modal was, therefore, used to assess the changes in body mass and body composition over time (baseline, pre-surgery, 4 and 8 weeks after surgery) controlling for the following factors: age, sex, baseline body mass index, baseline 6MWT, and mean postoperative compliance to the interventions. Mixed effects models are preferred to repeated measures analysis of variance because these models accommodate incomplete data while controlling for baseline variables [25]. The mixed effects model was used to assess the effects of group (rehabilitation as the reference value vs. prehabilitation), time (baseline as the reference value), and the interaction between group and time on change in body mass and body composition. All analyses were based on available data without imputation of missing values and performed using Stata 14.1 (2015, StataCorp).

3. Results

3.1. Pooled data

Data were similar and appropriate for pooling because no statistically significant differences greater than the pre-specified alpha of 0.05 were found at any timepoints between the two prehabilitation trials (Supplemental Table 1). Furthermore, the “study” variable was not a statistically significant predictor of change in LBM 8 weeks after surgery in the univariate ($P = 0.277$) and multiple regression models ($P = 0.487$) (Supplemental Table 2).

3.2. Missing data

Pooled data included 76 patients that followed prehabilitation and 63 patients that followed rehabilitation (total $n = 139$). A small amount of missing data were present for the pre-surgery measurement (LBM: 4 for prehabilitation, 7 for rehabilitation, total 8% missing). The missing data at 4 weeks after surgery included 17 observations for LBM (12 for prehabilitation, 9 for rehabilitation, total 12% missing). At 8 weeks after surgery missing data included 21 observations for LBM (8 for prehabilitation, 9 for rehabilitation, total 15% missing). Patient characteristics and outcomes for the missing sample were similar to the characteristics of the entire cohort, suggesting the data were missing completely at random (Supplemental Table 3).

3.3. Patient characteristics

No statistically significant differences were identified between pooled prehabilitation and rehabilitation groups at baseline in age, sex, anthropometrics, and surgery variables (Table 1). Mean total duration of prehabilitation was 33.7 days (95% CI: 29.4–37.9 days) and the preoperative duration for the rehabilitation group was 29.7 days (19.9–37.5 days). Mean compliance to the prehabilitation intervention was 88.3% (83.9–92.7%) before surgery. After surgery, mean compliance to the intervention was statistically greater in the prehabilitation group: 68.3% (62.1–74.7%) in the prehabilitation group and 54.3% (45.6–63.0%, $P = 0.009$ between groups) in the rehabilitation group.

3.4. Unadjusted analysis

Figures 1 and 2 depict the uncontrolled, crude analysis of mean changes in absolute lean and fat mass of colorectal cancer surgery patients following prehabilitation or rehabilitation. On average, prehabilitated patients experienced significant gains in LBM (change from baseline = +0.4 kg; 95% confidence interval: 0.03 to 0.7 to kg, $P = 0.031$) and lost FM (change from baseline = −0.6 kg, 95%CI: −1.0 to −0.2 kg, $P = 0.005$) in the pre-surgery period. In contrast, no significant preoperative changes were observed in LBM or FM of rehabilitated patients, compared to baseline. Prehabilitated patients also recovered their baseline LBM by the 8th postoperative week (change from baseline = −0.1 kg; 95%CI: −0.6 to 0.4 kg, $P = 0.659$). Rehabilitated patients did not recover their baseline LBM by the 8th postoperative week (change in baseline = −1.1 kg, 95%CI: −2.3 to −0.02 kg, $P = 0.045$).

Table 1
Pooled baseline demographic, clinical, and study characteristics of colorectal cancer surgery patients randomized to prehabilitation vs. rehabilitation at baseline.

	Pooled prehabilitation (n = 76)	Pooled rehabilitation (n = 63)	P-value
Age, years, mean (SD)	68.9 (12.1)	66.1 (10.3)	0.138
Male, n (%)	51 (67.1)	42 (66.6)	0.956
Weight, kg, mean (SD)	78.0 (15.2)	81.0 (13.6)	0.224
Body mass index, kg/m^2, mean (SD)	27.3 (4.3)	28.3 (4.1)	0.180
Lean body mass, kg, mean (SD)	54.4 (11.2)	55.5 (10.7)	0.578
Lean body mass, %, mean (SD)	69.9 (8.5)	68.6 (8.0)	0.389
Body fat mass, kg, mean (SD)	23.8 (8.6)	25.5 (7.9)	0.229
Fat mass, %, mean (SD)	30.1 (8.5)	31.3 (8.0)	0.386
Six-minute walk test, meters, mean (SD)	437 (118)	440 (96)	0.874
Open procedure, n (%)	8 (10.5)	7 (11.1)	0.886
Converted to open procedure, n (%)	3 (3.9)	6 (9.7)	0.175
Type of resection, n (%)			
Colon[a]	50 (65.8)	39 (61.9)	0.725
Rectum[b]	26 (34.2)	23 (36.5)	
Stoma	20 (26.3)	16 (25.3)	0.946
Time from recruitment to surgery, days, mean (95% CI)	33.7 (29.4–37.9)	29.7 (19.9–37.5)	0.289
Average intervention compliance before surgery, mean (95% CI)	88.3% (83.9–92.7%)	NA	NA
Average intervention compliance after surgery, mean (95% CI)	68.3% (62.1–74.7%)	54.3% (45.6–63.0%)	0.009

[a] Includes right- and left-hemicolectomy and sigmoid resection.
[b] Includes anterior resection, low anterior resection, and abdominoperineal resection.

3.5. Predictors of changes in total mass, absolute/relative lean, and fat mass in colorectal cancer patients

Tables 2 and 3 describe the effects of the predictors of pooled total mass, absolute and relative lean and fat mass for the colorectal cancer patients.

3.6. Total mass

Surgery was a significant predictor of altered body mass (Table 2); by the eight-postoperative week, total body mass had not returned to baseline levels (−2.22 kg; $P < 0.001$), independent of age, sex, baseline BMI, baseline 6MWT, and postoperative compliance to the interventions. Prehabilitation did not significantly alter body mass (no impact of group or group × time), compared to rehabilitation. Sex, baseline BMI and 6MWT were all predictors of total mass.

3.7. Lean and fat mass

In the mixed effects model, neither absolute/relative LBM nor FM were significantly different from baseline in the pre-surgery period (Tables 2 and 3). Absolute LBM and FM were significantly reduced at four weeks after surgery (LBM: −1.72 kg (0.37 kg), $P = 0.001$, FM: −1.32 kg (0.30 kg), $P < 0.001$) and at eight weeks after surgery (LBM: −1.41 kg (0.42 kg); $P = 0.001$; FM: −1.65 kg (0.34 kg), $P < 0.001$), compared to baseline. Relative FM differed from baseline at four (−0.70% (0.32%), $P = 0.027$) and at eight weeks after surgery (−1.26% (0.33%), $P < 0.001$). Group (i.e., prehabilitation vs. rehabilitation) did not significantly predict changes in absolute/relative LBM or FM over the eight-week period. However, the impact of prehabilitation on LBM and FM compared to rehabilitation *varied over time* (i.e., group × time). Compared to rehabilitated patients, prehabilitated patients had significantly *more* absolute/relative LBM which varied over the eight-week period: at four

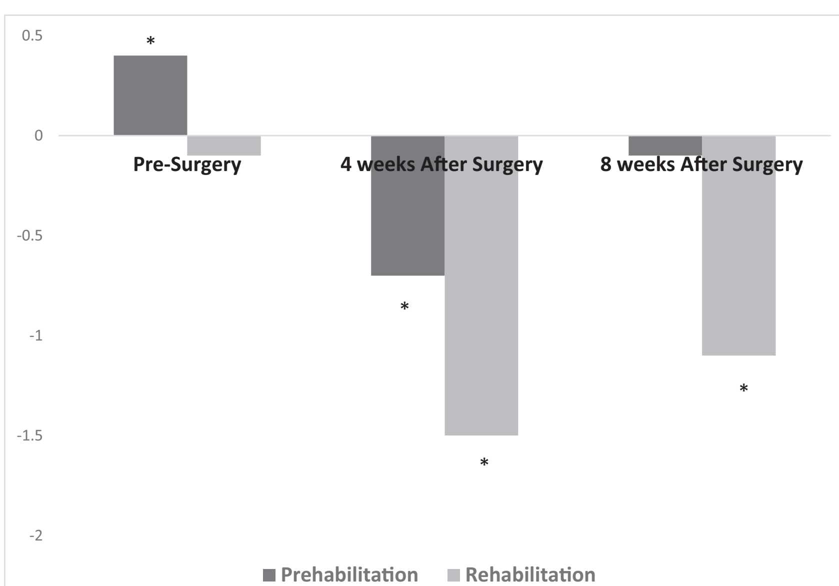

Fig. 1. Unadjusted mean changes in absolute lean mass of colorectal cancer surgery patients following prehabilitation or rehabilitation. *denotes statistically different compared to baseline ($p < 0.05$).

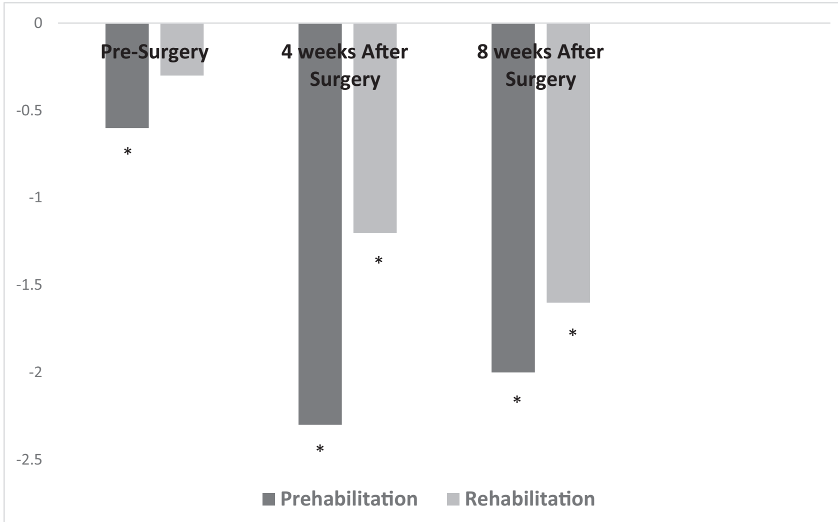

Fig. 2. Unadjusted mean changes in absolute fat mass of colorectal cancer surgery patients following prehabilitation or rehabilitation. *denotes statistically different compared to baseline ($p < 0.005$).

Table 2
Mixed effects model of pooled total mass, lean and fat mass for colorectal cancer surgery patients.

Predictor variables	Total mass (kg)		Absolute lean mass (kg)		Absolute fat mass (kg)	
	Regression coefficient (SE)	P-value	Regression coefficient (SE)	P-value	Regression coefficient (SE)	P-value
Group	−0.47 (1.22)	0.703	−0.30 (1.16)	0.796	−0.34 (0.67)	0.605
Time						
Pre-surgery	−0.33 (0.33)	0.314	−0.12 (0.35)	0.719	−0.32 (0.27)	0.246
4 weeks post-surgery	−2.54 (0.40)	<0.001	−1.72 (0.37)	<0.001	−1.32 (0.30)	<0.001
8 weeks post-surgery	−2.22 (0.51)	<0.001	−1.41 (0.42)	0.001	−1.65 (0.34)	<0.001
Group × time						
Pre-surgery	0.13 (0.42)	0.759	0.59 (0.46)	0.196	−0.35 (0.36)	0.322
4 weeks post-surgery	−0.26 (0.48)	0.591	1.22 (0.49)	0.013	−0.91 (0.39)	0.018
8 weeks post-surgery	0.22 (0.56)	0.699	1.55 (0.54)	0.004	−0.26 (0.43)	0.552
Age	−0.07 (0.06)	0.258	−0.11 (0.06)	0.040	0.03 (0.03)	0.336
Sex	10.75 (1.32)	<0.001	15.02 (1.25)	<0.001	−4.20 (0.66)	<0.001
Baseline BMI	2.46 (0.14)	<0.001	0.79 (0.13)	<0.001	1.66 (0.07)	<0.001
Baseline 6MWT	0.01 (0.006)	0.034	0.016 (0.006)	0.006	−0.004 (0.003)	0.209
Average postoperative intervention compliance	2.29 (7.3)	0.771	0.83 (1.79)	0.644	0.69 (0.95)	0.468

BMI is body mass index; 6MWT is six-minute walk test; Group refers to prehabilitation vs. rehabilitation (rehabilitation is the reference value); Time refers to the four-timepoints of measurement with baseline as the reference value; Group × time refers to the interaction between the dependent variable, time, and group. Age, BMI, 6MWT, and average postoperative intervention compliance are continuous variables. Sex is a dichotomous variable (female is the reference value).

Table 3
Mixed effects model of pooled relative lean and fat mass for colorectal cancer surgery patients.

Predictor variables	Relative lean mass (%)		Relative fat mass (%)	
	Regression coefficient (SE)	P-value	Regression coefficient (SE)	P-value
Group	0.68 (0.83)	0.412	−0.52 (0.81)	0.517
Time				
Pre-surgery	0.16 (0.37)	0.665	−0.09 (0.31)	0.763
4 weeks post-surgery	0.28 (0.40)	0.478	−0.70 (0.32)	0.027
8 weeks post-surgery	0.35 (0.45)	0.435	−1.26 (0.33)	<0.001
Group × time				
Pre-surgery	0.53 (0.49)	0.273	−0.56 (0.42)	0.181
4 weeks post-surgery	1.33 (0.52)	0.011	−0.99 (0.42)	0.020
8 weeks post-surgery	1.30 (0.57)	0.024	−0.17 (0.43)	0.693
Age	−0.10 (0.04)	0.010	0.07 (0.04)	0.056
Sex	9.82 (0.86)	<0.001	−9.67 (0.81)	<0.001
Baseline BMI	−1.20 (0.09)	<0.001	1.23 (0.09)	<0.001
Baseline 6MWT	0.01 (0.004)	0.005	−0.01 (0.004)	0.004
Average postoperative intervention compliance	−0.58 (1.23)	0.639	0.76 (1.17)	0.518

BMI is body mass index; 6MWT is six-minute walk test; Group refers to prehabilitation vs. rehabilitation (rehabilitation is the reference value); Time refers to the four-timepoints of measurement with baseline as the reference value; Group × time refers to the interaction between the dependent variable, time, and group. Age, BMI, 6MWT, and average postoperative intervention compliance are continuous variables. Sex is a dichotomous variable (female is the reference value).

weeks after surgery (+1.22 kg (0.49 kg), P = 0.013; +1.33% (0.52%), P = 0.011) and at eight weeks after surgery (+1.55 kg (0.54 kg), P = 0.004; +1.30% (0.57%), P = 0.024); totaling 0.9 kg and 2% more LBM than rehabilitated patients at four weeks and 1.3 kg and 2% more at eight weeks (i.e., group + group × time), independent of age, sex, baseline BMI, baseline 6MWT, and compliance to the postoperative interventions. Additionally, compared to rehabilitated patients, prehabilitated patients had significantly *less* absolute/relative FM at four weeks after surgery (−0.91 kg (0.39 kg), P = 0.018; −0.99% (0.42%), P = 0.020); totaling 1.3 kg and 1.5% less FM than rehabilitated patients at four weeks postoperatively. Sex and baseline BMI were independent predictors of both absolute LBM and FM. Age and baseline 6MWT were additional independent predictors of absolute LBM. Sex, baseline BMI, and baseline 6MWT were independent predictors of both relative LBM and FM. Age was an additional independent predictor of relative LBM.

4. Discussion

We previously conducted two RCTs on the impact of surgical trimodal prehabilitation versus rehabilitation on colorectal cancer patients [7,8]; by compiling individual patient data from these studies, we have obtained an overall description of a larger cohort of patients randomized to these interventions. Our findings indicate that trimodal prehabilitation interventions positively modulated body composition after colorectal surgery for cancer: prehabilitated patients had higher relative and absolute LBM at four and eight weeks post-surgery compared to rehabilitated patients. Prehabilitated patients also had lower relative and absolute FM at four weeks post-surgery. These findings were achieved independent of age, sex, baseline BMI, baseline fitness (as determined by 6MWT), and self-reported compliance to the intervention postoperatively. Furthermore, prehabilitated patients were more compliant than rehabilitated patients to the intervention prescription in the postoperative period, indicating that prehabilitated patients were actively engaged in health promoting behaviors (i.e., nutrition, exercise, and anxiety reduction) postoperatively.

Both prehabilitation and rehabilitation groups lost a significant amount of total mass, absolute lean and fat mass postoperatively, which is commonly observed after surgery. The post-surgical period is characterized by an elevation in protein turnover, whereby basal protein synthesis is unable to match catabolism, resulting in a negative net whole body protein balance [26] and the wasting of lean tissues (e.g., skeletal, respiratory, and gut) [27]. Using DXA, Phillips et al. reported that approximately 2 kg total lean mass was lost six weeks following uncomplicated hemicolectomy in a traditional surgical care setting [28]. Our findings are comparable, indicating that four-weeks post surgery, in an ERAS setting, our pooled cohort of patients lost nearly 2 kg of lean mass, and, therefore, suggests that the ERAS program does little to protect against typical post-surgical losses of LBM. A cohort study corroborates this finding; a cohort of colorectal surgical patients under ERAS care maintained LBM 8 days after surgery, compared with patients receiving *traditional* surgical care, but the ERAS cohort did not continue to maintain their LBM advantage at 28 days after surgery [29]. Given that the focus of the ERAS program is on the immediate perioperative period, this finding is not surprising and indicates that additional efforts are needed to optimize outcomes. Taken together, these findings suggest that prehabilitation interventions confer additional benefits that complement ERAS interventions, by promoting earlier recovery of LBM after colorectal surgery.

Prehabilitation attenuated the loss of surgically-induced catabolism. At four and eight weeks after surgery, prehabilitated patients had greater absolute and relative lean mass than rehabilitated patients. It is important to note that a rehabilitation intervention is *not* part of standard of care for colorectal surgery in traditional or ERAS care surgical settings; we would, thus, expect the magnitude of difference between prehabilitation and standard of care to be even greater. Protecting lean tissue is an important part of the cancer care course. Muscle, a large component of LBM, plays an important role in the successful progression and completion of oncological treatments (e.g., tolerance to chemotherapy), functional independence, quality of life, and overall survival of cancer patients [11,30–33]. In fact, muscle wasting is an independent adverse prognostic indicator in cancer [34–36], and maintenance of muscle mass is increasingly recognized as a therapeutic target for cancer care [12]. Our findings, therefore, suggest that surgical prehabilitation plays a role in the cancer care course for colorectal patients by attenuating the loss of lean tissue typically observed post-surgery.

Several authors have hypothesized that prehabilitation strengthens preoperative functional reserve and thus serves as a “buffer” against the potentially detrimental effects of surgical stress and postsurgical immobility [5,37]. Interestingly, our mixed effects analysis suggested that prehabilitation did not alter preoperative body composition. It is probable that four weeks of exercise-training and whey protein supplementation is insufficient to reveal *important gains* in LBM that can be detected by BIA. In point, a body composition study in which measurements were performed by both dual X-ray absorptiometry (DXA) (considered the gold standard measurement for body composition) and BIA before and after a 21-week training intervention in women, revealed that, compared to DXA, BIA underestimated the changes in body composition accrued with training [38]. The authors also found that the small changes in body composition produced by exercise-training could not be detected with BIA. It is therefore unclear whether four weeks of trimodal prehabilitation was insufficient to produce marked changes in body composition before surgery or whether a small change could not be sufficiently detected with BIA. Our findings support the latter argument; prehabilitation attenuated the loss of lean mass post-surgery, independent of post-operative intervention (i.e., rehabilitation) compliance. This finding suggests that it is the prehabilitation intervention itself, as hypothesized, that promotes an earlier LBM recovery.

Previous studies have identified that prehabilitation promotes an earlier return to functional capacity [6,23] compared with rehabilitation [7] and standard ERAS care [39]. We have now additionally identified that prehabilitation promotes superior post-surgery body composition as well as greater adherence to the post-surgery trimodal intervention, compared with rehabilitation. Altogether, these findings suggest that prehabilitation interventions might award additional, longer-term benefits, including promoting an earlier return to intended oncological treatment [40] and cancer survivorship [41], which should be studied. For instance, a recent systematic review of 100 studies identified that patients who exercised following a cancer diagnosis, compared to those who did not exercise or reported less exercise, were observed to have lower relative risk of cancer mortality, cancer recurrence, and experienced fewer adverse treatment-related side effects, such as fatigue [42]. The benefits of prehabilitation might thus extend beyond the perioperative period and should be investigated further.

A limitation of our study is that we had a high proportion of missing data (>10%) for the 4 and 8-week body composition measurements. However, the missing data were not preferentially lost to any one group, and patient outcomes were not different. A second limitation is that the rehabilitated patients were aware of the study objective and may have begun instituting exercise and nutritional changes in the preoperative period, which could have underestimated the comparative benefit of prehabilitation. Lastly, when compared to DXA, BIA underestimates the changes in body composition accrued with exercise training [38], and thus due to methodological limitations we may have underestimated the impact of prehabilitation on body composition.

In conclusion, trimodal prehabilitation positively modulated the body composition of colorectal cancer patients such that they did not experience the degree of loss in postoperative lean body mass observed with rehabilitation. Offering a prehabilitation program to colorectal cancer patients awaiting resection is a useful strategy to mitigate the impact of the surgical stress response on lean tissue in an Enhanced Recovery After Surgery setting.

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Conflict of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.06.982.

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