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Functional capacity of prediabetic patients: effect of multimodal prehabilitation in patients undergoing colorectal cancer resection

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ABSTRACT

Background: Prehabilitation is the process of increasing functional capacity (FC) before surgery. Poor glycemic control is associated with worse outcomes in patients undergoing surgery. Therefore, prediabetic patients could particularly benefit from prehabilitation.

Methods: This is a pooled analysis of individual patient data from three multimodal prehabilitation trials in colorectal cancer surgery. Following a baseline assessment using the 6-minute walking test (6MWT), subjects were randomized to multimodal prehabilitation or to a control group. Participants were reassessed 24 h before surgery and 4 weeks after surgery. Prediabetes (PreDM) was defined as HbA1c 5.7%–6.4%. Multivariable logistic regression was used to adjust for potentially confounding variables.

Results: Participation in a prehabilitation program was the most important predictive factor of clinical improvement in FC prior to surgery (Adjusted OR 2.42, 95% CI 1.18, 4.94); prediabetes was not a statistically significant predictor of improvement in FC after adjustments for covariates. Prehabilitation attenuated the loss of FC in unadjusted analyses after surgery in prediabetic patients (PreDM Control: median change −6 m [IQR −50–20] vs PreDM Prehab: median change +25 m [IQR −20–53], $p = 0.045$). Adjusted analyses also suggested the protective effect against loss of FC after surgery was stronger in prediabetic patients (PreDM Prehab vs PreDM Control: OR 5.5, 95% CI: 1.2–25.8; Normo Prehab vs Normo Control: OR 1.5, 95% CI: 0.53–4.52).

Conclusions: Multimodal prehabilitation favored clinical recovery of FC after surgery in CRC patients, especially prediabetic patients.

Abbreviations: 6MWD: 6-minute walked distance; 6MWT: 6-minute walk test; BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CRC: colorectal cancer; CRP: C-reactiveprotein; CVD: cardiovascular disease; ERAS: Enhanced Recovery After Surgery; FC: functional capacity; HbA1c: glycated hemoglobin; HOMA-IR: homeostasis model assessment of insulin resistance; IL-6: interleukin 6; IQR: interquartile range; LBM: lean body mass; OR: odds ratio; OSA: obstructive sleep apnea; PreDM: prediabetes; Prehab: prehabilitation; RCT: randomized controlled trials; RM: range of motion; TNF-α: tumor necrosis factor alpha

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Introduction

Functional capacity (FC) reflects the ability of individuals to perform activities of daily living, and is determined by the integrity of the pulmonary, cardiovascular, and musculoskeletal systems [1,2]. Poor baseline FC has been shown to increase the risk of complications after major non-cardiac surgery and prolongs recovery after abdominal surgery [3].

Prehabilitation is the process of increasing FC before surgery in order to facilitate the return to baseline functional status [4]. A first randomized clinical trial of prehabilitation in colorectal surgery showed that exercise alone is not sufficient to attenuate the stress response induced by surgery [5]. Prehabilitation programs have since evolved to target all known risk factors for postoperative complications, namely poor FC, suboptimal nutritional status, cigarette smoking and psychological distress [6–8].

Poor preoperative glycemic control and insulin resistance are often observed in patients with colorectal cancer (CRC) [9] and the prevalence of prediabetes in surgical patients is approximately 23% [10]. A recent systematic review suggests that elevated pre-operative glycated hemoglobin (HbA1c) levels among non-diabetic patients might be associated with an increased risk of post-operative complications, including after colorectal surgery [11,12]. Physical activity and nutritional optimization are recognized modulators of insulin resistance and glycemic control [13]. Yet, the impact of multimodal prehabilitation on prediabetic patients is still poorly understood in the context of surgery.

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Supplemental data for this article can be accessed here.

The main objectives of this exploratory study involving patients undergoing CRC resection for non-metastatic cancer, were 1) to characterize perioperative functional capacity of patients with prediabetes versus normoglycemic patients, and 2) to determine the effect of prehabilitation on postoperative FC in prediabetic patients.

Material and methods

Study population

This study is a secondary analysis of pooled data arising from two published randomized controlled trials (RCT) [8,14], one non-randomized interventional study [15] and one ongoing RCT (Netherlands Trial Register: NTR5947) on the effect of prehabilitation on functional capacity before and after colorectal cancer surgery. All studies were approved by the McGill University Health Center (MUHC) Research Ethics Board and all enrolled study subjects signed a consent form prior to the beginning of the studies. Prediabetes was defined with HbA1c between 5.7% and 6.4% at baseline, as per American Diabetes Association's definition [16]. For the purpose of this study, patients were excluded from the present secondary analyses if they were type 1 or 2 diabetics.

Following a baseline assessment of anthropometrics and FC, patients were allocated either to the prehabilitation group, receiving 4 weeks of supervised prehabilitation, or to the control group, receiving only standard of care as per ERAS guidelines [17]. Patients' FC, nutritional status and anthropometrics were assessed at baseline, 24–48 h before surgery, and 4 weeks after surgery.

Prehabilitation intervention

The multimodal prehabilitation arm received exercise training, nutritional counseling and supplementation, and anxiety relaxation over the four weeks prior to their surgery. The exercise training was supervised by a licensed kinesiologist and performed at the prehabilitation clinic one to three times per week for 4 weeks. The supervised aerobic training was performed on a stationary bicycle and consisted of four bouts of two-to-three minutes at high intensity interspersed by three bouts of four minutes of active recovery at moderate intensity. The resistance training program consisted of eight exercises targeting all major muscle groups of the body, performed for two sets of 10 repetitions. Intensity of resistance training was based on 1-RM strength tests performed at baseline. The decision of supervised training sessions was based on the evidence that supervised exercise training led to greater changes in functional capacity compared to homebased exercise training [18].

Following a consultation with a nutritionist, patients received a personalized dietary intervention with the objective of preventing perioperative malnutrition and to enhance the anabolic effect of physical training and improve fat-free mass during the prehabilitation period. Based on estimated habitual protein intake, participants received tailored dietary advices to get a daily protein intake of 1.5 gram/kg of body weight, with supplemental whey protein (Immunocal®; Immunotec Inc., Vaudreuil, Quebec, Canada), if needed. To stimulate muscle protein synthesis, participants were provided with 20–30 grams of whey protein immediately after their supervised exercise sessions [19].

A relaxation specialist met with participants to teach and prescribe breathing and imagery exercises for stress-reduction purposes. This specialist also addressed the patient's anxieties, coping strategies, and post-operative expectations, with the goal of optimizing psychological well-being and ways of coping with surgery. The importance of the patient's active participation in the healing process was also discussed.

Outcome measures

The primary outcome, functional capacity, was measured using the 6-minute walk test (6MWT) at baseline, just before surgery and 4 weeks after surgery. Briefly, subjects were instructed to walk back and forth, in a 20 m stretch of hallway, for six minutes, at a pace that would make them tired by the end of the walk. Encouragement and feedback were given according to published guidelines [20]. Patients were allowed to rest during the test if needed, but this time was included in the 6 min. The 6MWT has been shown to be reliable and valid in various populations including the colorectal surgery population [21]. The minimal clinically important difference for the 6MWT has been estimated (using anchor-based methods) at 19 m for comparisons between groups [22]·

Body weight (kg), fat-free mass (kg), and body fat percentage were measured at each visit using a multi-frequency bioelectrical impedance analysis (InBody 230 V®). Body mass index (BMI) was calculated as follows: BMI (kg/m^2) = [body weight/height^2]. Glycated hemoglobin (HbA1c), hemoglobin, albumin and C-reactive protein (CRP) concentrations were collected from patients' medical records as part of the usual pre-surgical assessment at the MUHC.

Statistical analyses

Shapiro-Wilk normality tests were used to evaluate the distribution of continuous variables. If the distributions were not normal, the non-parametric Mann-Whitney U tests were used to examine differences between prediabetics and normoglycemics for continuous variables. Chi-Square tests were used to examine differences between prediabetic and normoglycemic patients for categorical variables. Data are presented as median and interquartile range (IQR) unless stated otherwise.

We conducted a complete case analysis to examine the impact of metabolic status and prehabilitation on FC before surgery, and 4 weeks after surgery. The unadjusted changes in performance on the 6MWT since baseline were compared at each visit among 4 groups (normoglycemics patients in control group, normoglycemics in prehabilitation, prediabetics in control group, prediabetics in prehabilitation) using non-parametric Kruskal Wallis tests. Post hoc Bonferroni tests were performed to correct for multiple comparisons. Chi-Square tests were used to compare the proportions of patients who improved their FC by more than 19 m pre-operatively, and the proportions of patients who improved their baseline FC after surgery among the same 4 groups. Post hoc Bonferroni tests were performed to correct for multiple comparisons. Missing data were excluded from these statistical analyses.

To control for the potential influence of confounding variables on our primary outcome, mixed effects logistic regressions were then used to evaluate the relationship of prehabilitation on clinical improvement (i.e. change ≥19 m since baseline) in FC before surgery, and recovery of FC after surgery (within 19 m of baseline). The full models were adjusted to account for predictors of FC and for differences in baseline variables between groups that were also considered potential independent predictors of FC based on literature review (age, gender, baseline BMI, chronic obstructive pulmonary disease (COPD) and baseline FC) [23–25]. To account for the potential random effects of each individual study that was pooled, the study variable was included in the models as a random effect variable. All statistical analyses were performed using IBM SPSS Statistics 26 for Windows, and results were considered statistically significant when $p < 0.05$.

Results

Baseline characteristics of prediabetic and normoglycemic patients

Data from 121 prediabetic patients and 90 normoglycemic patients were included in the study. Baseline anthropometric and metabolic parameters are presented in Table 1. No statistically significant differences were noted between the groups in terms of gender, smoking status, alcohol consumption, tumor stage and type, and history of neoadjuvant therapy for cancer. Similarly, no differences were observed between groups for fat-free mass (kg), medical history of COPD, OSA, CVD, dyslipidemia, anemia and albumin concentration.

Prediabetic patients had a higher HbA1c than normoglycemic patients. They were also older, more overweight and had a higher percentage of body fat. Prediabetic patients had a higher prevalence of hypertension and higher concentrations of CRP than normoglycemic patients (although median for both groups were below 10 mg/L). Functional capacity at baseline was 475 m [IQR 354–535] for prediabetics vs 488 m [IQR 391–573] for normoglycemics $p = 0.03$. However, no statistical difference was observed between groups once the performance on the 6MWT was corrected for age and sex (i.e. predicted 6MWT).

Baseline characteristics of patients who were lost to follow up after surgery

For the 6MWT, 14% ($n = 30/211$) of the preoperative values and 27% ($n = 58/211$) of the postoperative values were missing. Baseline anthropometric and metabolic parameters of patients who were lost to follow up after their surgery are presented in Supplementary Table S1. Compared to the patients who were included in the postoperative analyses ($N = 153$), patients who were lost to follow up after surgery ($N = 58$) were older (median age 76 [IQR 69–81] vs 69 [IQR 57−76], $p = 0.003$), had a slightly lower HbA1c (median 5.6% [IQR 5.2–5.9] vs 5.7% [IQR 5.5–6.1], $p = 0.03$), and had a poorer functional capacity at baseline (median 465 m [IQR 328–522] vs 484 [IQR 391–555], $p = 0.02$). There was no statistical difference between groups regarding the proportion of prediabetics and the proportion of patients who received prehabilitation prior to their surgery.

Stratified analyses showed that normoglycemic patients who were lost to follow were older compared to normoglycemics who were included in the postoperative analyses (median 74 [IQR 70–82] vs 61 [IQR 48–74], respectively), and that they had a poorer performance on their baseline 6MWT (median 399 m [IQR 287–525] vs 525 m [IQR 430–619], respectively). There was no statistical difference in age and baseline 6-minute walked distance (6MWD) among prediabetic patients who were included in the analyses compared to those who were lost to follow up.

Table 1. Baseline characteristics of study sample and groups based on metabolic status.

	Metabolic status		
Variable	Normo ($N = 90$)	Prediabetic ($N = 121$)	p Value*
Demographic variables			
Age (years)	67.0 (51.0, 78.0)	74.0 (66.0, 79.5)	0.001
Age > 65 (*N*, %)	46 (51.1)	92 (76.0)	<0.001
Gender (Male; *N*, %)	41 (46.6)	68 (43.3)	0.15
Body Composition			
Weight (kg)	68.8 (56.7, 78.5)	74.1 (63.5, 85.2)	0.008
BMI (kg/m^2)	24.3 (21.7, 27.9)	27.2 (24.8, 30.0)	<0.001
LBM (kg)	46.5 (40.1, 57.2)	47.7 (39.5, 57.5)	0.54
Body fat (%)	28.6 (22.0, 36.1)	33.6 (26.7, 38.2)	0.002
Comorbidities (*N*, %)			
Hypertension	26 (28.9)	54 (44.6)	0.02
COPD	17 (18.9)	29 (24.0)	0.38
OSA	3 (3.3)	12 (10.1)	0.06
CVD	14 (15.6)	29 (24.0)	0.13
Dyslipidemia	10 (11.1)	23 (19.2)	0.11
Current smoker (*N*, %)	10 (11.1)	18 (14.9)	0.43
Alcohol consumption (*N*, %)	43 (47.8)	56 (46.3)	0.83
Cancer-related variables (*N*, %)			
Tumor stage ≥3	28 (43.1)	29 (31.5)	0.14
Type of tumor (Colon)	64 (76.2)	90 (75.6)	0.93
Neoadjuvant therapy	15 (18.1)	19 (16.7)	0.80
Clinical characteristics			
HbA1c (%)	5.4 (5.1, 5.5)	5.9 (5.8, 6.1)	<0.001
Alb	42 (38, 44)	41 (38, 43)	0.34
Hb	129 (113, 141)	131 (114, 142)	0.80
CRP (mg/L)	2.7 (0.7, 7.5)	4.0 (1.4, 9.1)	0.02
Six-minute walking test			
6MWD (m)	488 (391, 573)	475 (354, 525)	0.03
6MWD (% predicted)	74.3 (65.4, 88.3)	72.5 (59.9, 83.8)	0.21
6MWD < 300 m (*N*, %)	9 (10.0)	18 (14.9)	0.59
6MWD > 400 m (*N*, %)	64 (71.1)	83 (68.6)	0.60
Randomized to prehab (*N*, %)	65 (72.2)	83 (68.6)	0.57
Supervised 1x/wk (*N*, %)	28 (31.1)	47 (38.8)	0.22
Supervised 3x/wk (*N*, %)	37 (41.1)	36 (29.8)	0.21

*p Value for normo vs prediabetic. Data are expressed as median (IQR) unless indicated otherwise.
BMI: body mass index; LBM: lean body mass; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; OSA: obstructive sleep apnea; HbA1c: glycated hemoglobin; Alb: albumin; Hb: hemoglobin; CRP: c-reactive protein; 6MWD: 6-minute walked distance; Normo: normoglycemics; Prehab: prehabilitation.

Patients who were in the control group and were lost to follow were older compared to control patients who were included in the postoperative analyses (median 78 [IQR 74–84] vs 72 [IQR 57–82], respectively), and had a lower HbA1c at baseline (median 5.6 [IQR 5.2–5.7] vs 5.8 [IQR 5.5–6.1], respectively). There was no statistical difference in age and baseline 6MWD among patients randomized to prehabilitation who were included in the postoperative analyses compared to those who were lost to follow up.

Unadjusted change in FC in normoglycemic and prediabetic patients by intervention

Figure 1 illustrates the pre and postoperative changes, as compared with baseline, in 6MWD of normoglycemic and prediabetic patients according to the type of intervention received before their colorectal surgery. Both prehabilitated groups similarly improved 6MWD, compared to control, in the preoperative period ($p > 0.05$ after consideration for multiple comparisons).

Normoglycemic and prediabetic patients who received prehabilitation maintained their FC after surgery (Normoglycemic Prehab: median change +2 m [IQR −22–33]; PreDM Prehab: median change +25 m [IQR −20–53]), whereas patients who did not receive prehabilitation had a lower performance on the 6MWT after their operation (Normoglycemic Control: median change −31 m [IQR: −65–13]; PreDM Control: median change −6 m [IQR −50–20]). The postsurgical change in FC observed in prediabetic patients who had received prehabilitation prior to their surgery was higher compared to patients who were randomized to the control groups (PreDM prehab vs PreDM control, $p = 0.045$; PreDM prehab vs Normoglycemic Control, $p = 0.02$).

The proportions of patients who improved their baseline FC before surgery were not statistically different between the 4 groups based on metabolic status and type of intervention (see Supplementary Table S2). However, the proportion of patients who improved their baseline FC after surgery was statistically higher among prehabilitated prediabetic patients compared to prediabetic patients in the control group (52.2% vs 23.2%, respectively, $p < 0.05$).

Odds of improving preoperative FC by 19 meters or more

Table 2 presents the effect of prehabilitation and metabolic status on preoperative FC, adjusted for possible confounding factors. Overall, participation in a prehabilitation program was the most important predictive factor of clinical improvement in FC (OR 2.42, 95% CI 1.18–4.94). Age (OR 0.96, 95% CI 0.93–0.99) and baseline 6MWD (OR 0.99, 95% CI 0.99–0.99), as continuous variables, also predicted improvement in FC prior to surgery. Prediabetes was not considered a statistically significant factor of improvement in FC after adjustments for other covariates. When improvement in FC was stratified by metabolic status, preoperative benefits of prehabilitation were statistically significant only in prediabetic patients (OR 3.16 (95% CI 1.19–8.39) vs normoglycemic patients OR 1.72 (95% CI 0.41–7.33)).

Odds of recovering FC after surgery

Table 3 presents the effect of prehabilitation and metabolic status on postoperative FC, adjusted for possible confounding factors. Univariate analyses (data not shown), revealed that the odds a patient recovered FC after surgery were 2.2 times greater in those who received prehabilitation compared to control. When recovery of FC was stratified by glycemic status, univariate analyses suggested that the odds prediabetic patients recovered FC after surgery were 4.2 times higher with prehabilitation than with the control (95% CI 1.0–19.0); whereas the odds normoglycemic patients recovered FC after surgery were 1.7 times higher in prehabilitated patients relative to controls (95% CI 0.6–4.9, data not shown). Adjusted analyses (Table 3), produced similar

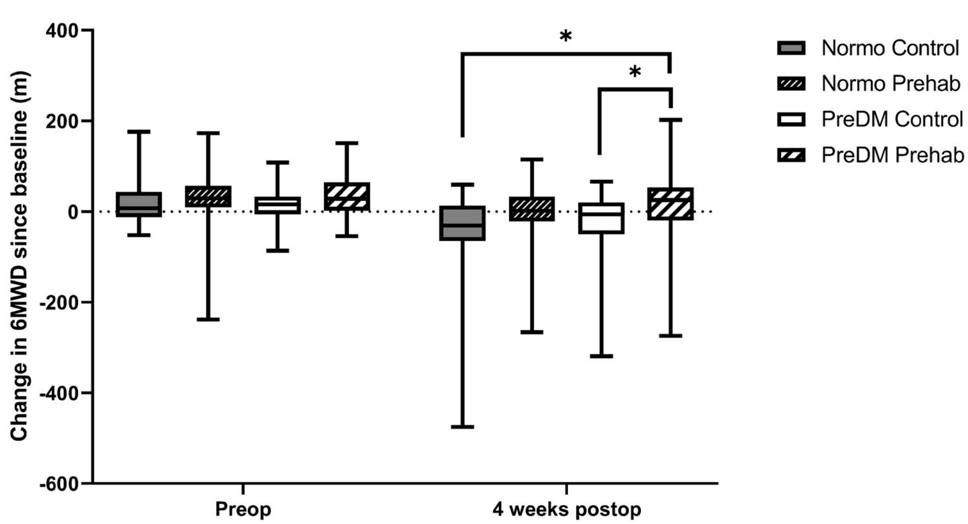

Figure 1. Preoperative and postoperative unadjusted changes in 6MWD of normoglycemic and prediabetic patients by intervention group. Boxes represent medians with interquartile ranges. Whiskers represent minimal and maximal value. *Corrected $p < 0.05$ vs PreDM prehab at same time point.
6MWD, 6-minute walked distance; Preop, preoperative visit; Postop, postoperative visit; PreDM, prediabetic; Normo, normoglycemic; Prehab, prehabilitation.

Table 2. Odds of improving preoperative FC by 19 meters or more.

	All patients ($N = 179$)	Prediabetics ($n = 108$)	Normoglycemics ($n = 71$)
Variable	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Prehabilitation	2.42 (1.18–4.94)	3.16 (1.19–8.39)	1.72 (0.41–7.33)
Prediabetes	0.70 (0.35–1.41)	–	–
Age	0.96 (0.93–0.99)	0.96 (0.92–1.01)	0.94 (0.88–1.00)
Female sex	1.86 (0.97–3.55)	1.60 (0.64–3.99)	1.33 (0.43–4.08)
BMI	1.00 (0.94–1.06)	1.02 (0.93–1.11)	0.99 (0.90–1.09)
Baseline 6MWD	0.99 (0.99–0.99)	1.00 (0.99–1.00)	0.99 (0.99–1.00)
COPD	0.52 (0.19–1.44)	0.49 (0.12–2.00)	0.88 (0.12–6.76)

FC: functional capacity; BMI: body mass index; 6MWD: 6 min walked distance; COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval. For each variable, the *adjusted OR* corresponds to the OR adjusted for all other variables listed in the table. Age, BMI, and baseline 6MWD are continuous variables: the reported ORs refer to the effect of increasing age by 1 year, BMI by 1 kg/m^2, and 6MWD by 1 m. Prediabetes, prehabilitation, female sex, and COPD are dichotomous variables (0 is the reference).

Table 3. Odds of recovering FC after surgery.

	All patients ($n = 153$)	Prediabetics ($n = 93$)	Normoglycemics ($n = 60$)
Variable	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Prehabilitation	2.55 (1.11–5.85)	5.55 (1.2–25.8)	1.56 (0.53–4.52)
Prediabetes	0.75 (0.32–1.73)	–	–
Age	0.98 (0.94–1.01)	0.95 (0.89–1.01)	0.98 (0.93–1.03)
Female sex	1.18 (0.53–2.63)	0.42 (0.09–1.81)	1.65 (0.56–4.88)
Baseline BMI	0.97 (0.90–1.05)	0.97 (0.86–1.10)	0.95 (0.85–1.06)
COPD	0.22 (0.07–0.73)	0.83 (0.09–8.15)	0.12 (0.02–0.58)
Baseline 6MWD	0.99 (0.98–0.99)	0.98 (0.97–0.99)	0.99 (0.98–0.99)

FC: functional capacity; BMI: body mass index; COPD: chronic obstructive pulmonary disease; 6MWD: 6-minute walked distance; OR: odds ratio; CI: confidence interval. For each variable, the *adjusted OR* corresponds to the OR adjusted for all other variables listed in the table. Age, BMI, and baseline 6MWD are continuous variables. The reported ORs refer to the effect of increasing age by 1 year, BMI by 1 kg/m^2, and 6MWD by 1 m. Prediabetes, prehabilitation, female sex and COPD are dichotomous variables (0 is the reference).

findings: the odds prediabetic patients recovered FC after surgery were 5.5 times higher with prehabilitation than with the control (95% CI 1.2–25.7).

Discussion

The aim of this study was to compare the metabolic and functional characteristics of prediabetic and normoglycemic CRC patients and to determine whether both groups derive the same benefits from multimodal prehabilitation (composed of 4 weeks of strength and high intensity interval training, nutritional optimization and supplementation, smoking cessation and psychological support). Interestingly, compared to controls, the odds that prehabilitated prediabetic patients recovered their baseline FC after surgery was 3 times that of normoglycemic patients who received prehabilitation prior to their surgery (Adjusted OR 5.5 vs OR 1.6, respectively). In adjusted analyses, the postoperative protective effect of prehabilitation was not statistically significant in normoglycemic patients.

Median FC at baseline was lower in prediabetic patients and is consistent with previous works from Astrom et al. [26] and Sayer et al. [27], who showed that impaired glucose metabolism is related with impaired physical function. On the other hand, Hiltunen et al. studied the association between functional status and glucose tolerance in non-institutionalized elderly individuals with conflicting results. Indeed, a first cross-sectional study, published in 1996 [28], did not show any statistically significant association between impaired glucose tolerance and functional capacity assessed by a questionnaire (OR 1.0, 95% CI 0.6–1.8). Yet, a follow-up study [29] conducted on the same population demonstrated that patients with impaired glucose tolerance had weaker abdominal muscles compared to subjects with normal glucose tolerance ($p = 0.001$). In our study, FC was assessed using the 6MWT, which is a validated, widely recognized submaximal test that evaluates the global responses of all systems involved during exercise, including the pulmonary and cardiovascular systems, neuromuscular function, and muscle metabolism. This test has also been shown to predict complications after a colorectal surgery [30].

Our results showed that multimodal prehabilitation improved FC of CRC patients in the 4-week period leading to surgery. Interestingly, prediabetic patients appeared to benefit the most from prehabilitation. This could be in part because they had a lower median FC at baseline, as suggested by Minnella et al. [25], but mostly because of the important relative differences in the 6MWD between prehabilitated prediabetics and prediabetic patients who were in the control group. The relative difference in the performance on the 6MWT among prehabilitated normoglycemics and patients who were in the control group was not nearly as great.

Previous publications suggest that even with adequate skeletal muscle mass, patients with impaired glucose metabolism (as observed in prediabetes) tend to have reduced muscle quality and function [31], a phenomenon that could be explained by ectopic fat deposition and secondary lipotoxicity in the skeletal muscles [32]. Peripheral neuropathy, a microvascular diabetic complication also observed in the prediabetes stage [33] might also contribute to the impairment of skeletal muscles function despite similar muscle mass. Finally, systemic inflammation, even at subclinical levels, has been associated with increased functional disability [34]. Future research should examine whether improvement in muscle function, systemic inflammation and glucose metabolism could explain why multimodal prehabilitation favors clinical recovery of FC in prediabetic patients.

Our findings might be limited by variations between the original RCTs' protocols, and by limitations inherent to secondary analyses. The analyses of longitudinal outcomes were also performed "per protocol" (i.e. using only the data from patients who completed the study as planned), such that the results do not reflect the real-life scenario in which some participants are lost during the follow-up. Normoglycemic patients who were lost to follow up were older and had a poorer performance on the 6MWT, which could have resulted in an overestimation of our findings in prediabetic patients; however, the proportions of prediabetics and of patients who received prehabilitation, both of which were our variables of interest, were not different among patients who were lost to follow up and those who were included in our analyses. Several potential confounding variables were not examined in the present study. First, the proportions of visceral and subcutaneous adipose tissue were not examined in our patients. Similarly, no data were collected regarding changes in glucose metabolism/insulin resistance and inflammatory status throughout the perioperative period. Despite the longitudinal nature of the initial RCTs, our analyses do not provide information regarding the temporal nature of the relationship between prediabetes and perioperative functional capacity; thus, the findings should be considered exploratory only. In addition, given the high percentage of missing data, and small sample sizes upon stratification (producing wide, imprecise confidence intervals), the postoperative findings should be cautiously considered exploratory. The choice of HbA1c to identify prediabetic patients was determined by the availability of the data and the clinical applicability of the results. Yet, proper assessment of insulin resistance using the gold-standard euglycemic-hyperinsulinemic clamp [35] or surrogate indexes such as the homeostasis model assessment (HOMA-IR) [36] or the more dynamic Matsuda Index [37] would have been more mechanistically accurate and constitute future research opportunities. Finally, slight variation in study protocols regarding the exercise intervention (once-per-week vs three-time-per-week, in-hospital training sessions) may have influenced the likelihood of improving FC during the perioperative period, however this was accounted for in our mixed effects model as a random variable. Future research should examine whether the frequency of supervised training influences the trajectory of FC and the metabolic status of patients throughout the perioperative period. Whether changes in FC and glucose metabolism among patients with CRC are mainly attributed to increased physical activity level, improved nutritional status, or the synergic effect of both lifestyle modifications should also be explored.

Conclusion

In conclusion, prediabetic patients had a lower median functional walking capacity at baseline compared to normoglycemic patients with CRC, and multimodal prehabilitation favored clinical recovery of FC in CRC patients, especially prediabetic patients.

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Author contributions

K.C. acquired, analyzed, and interpreted the data; wrote the manuscript; and approved the final version to be published. C.G. analyzed, and interpreted the data, wrote the manuscript and approved the final version to be published. R.A, G.B, V.F and E.M. edited and revised the manuscript, and approved the final version to be published. F.C designed the research, edited and revised the manuscript, and approved the final version to be published.

Disclosure statement

The authors declare no conflict of interest.

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