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Review Article

REVIEW ARTICLE

Prehabilitation, enhanced recovery after surgery, or both? A narrative review

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Summary

This narrative review presents a biological rationale and evidence to describe how the preoperative condition of the patient contributes to postoperative morbidity. Any preoperative condition that prevents a patient from tolerating the physiological stress of surgery (e.g. poor cardiopulmonary reserve, sarcopaenia), impairs the stress response (e.g. malnutrition, frailty), and/or augments the catabolic response to stress (e.g. insulin resistance) is a risk factor for poor surgical outcomes. Prehabilitation interventions that include exercise, nutrition, and psychosocial components can be applied before surgery to strengthen physiological reserve and enhance functional capacity, which, in turn, supports recovery through attaining surgical resilience. Prehabilitation complements Enhanced Recovery After Surgery (ERAS) care to achieve optimal patient outcomes because recovery is not a passive process and it begins preoperatively.

Keywords: enhanced recovery pathway; fast-track; injury; nutrition; perioperative; prehabilitation; preoperative; stress response; surgical risk

Postoperative morbidity and mortality are largely the product of the *preoperative condition* of the patient, the *quality of surgical care* provided, and the *degree of surgical stress elicited*.[1,2] This narrative review explores these three components to highlight the potential contribution of *prehabilitation* to patient recovery in modern surgical practices.

Surgical stress elicited

Surgical injury elicits a physiological response, known as the surgical stress response (Fig. 1). Afferent nerves and cytokines stimulated as a result of injury activate the hypothalamic–pituitary–adrenal axis and sympathetic nervous system producing integrated endocrine, haemodynamic, and immune responses to re-establish the body's dynamic steady state.[3,4] The endocrine response alters intermediary metabolism, catabolising body protein to support energy production and synthesis of inflammatory proteins (e.g. fibrinogen, a positive acute phase protein involved in wound healing), and manifests clinically as hyperglycaemia and body protein catabolism.[5] The haemodynamic response maintains plasma volume and cardiovascular homeostasis, and supports an elevated oxygen demand; clinically, this response might be observed as hypertension, tachycardia, urinary retention, and oedema. The immune response involves local and systemic inflammatory responses, mediated by a complex interplay of both pro- and anti-inflammatory cytokines, with the aim of reducing tissue damage, eliminating infections, and initiating the healing process.[4] For an excellent review of the surgical stress response, see Cusack and Buggy.[6]

The physiological response to surgery is believed to be an innate survival mechanism designed to re-establish homeostasis (i.e. body structure and function) as early as possible after injury; however, an inadequate, exaggerated, or prolonged stress response can lead to adverse outcomes[7] including catabolism of body protein.[8] Modern perioperative interventions aim to moderate the surgical stress response to minimise the negative effects produced, including catabolism, while maintaining the natural purpose of the stress response, which is to return the body to a state of 'normal' structure and function (i.e. homeostasis).[7]

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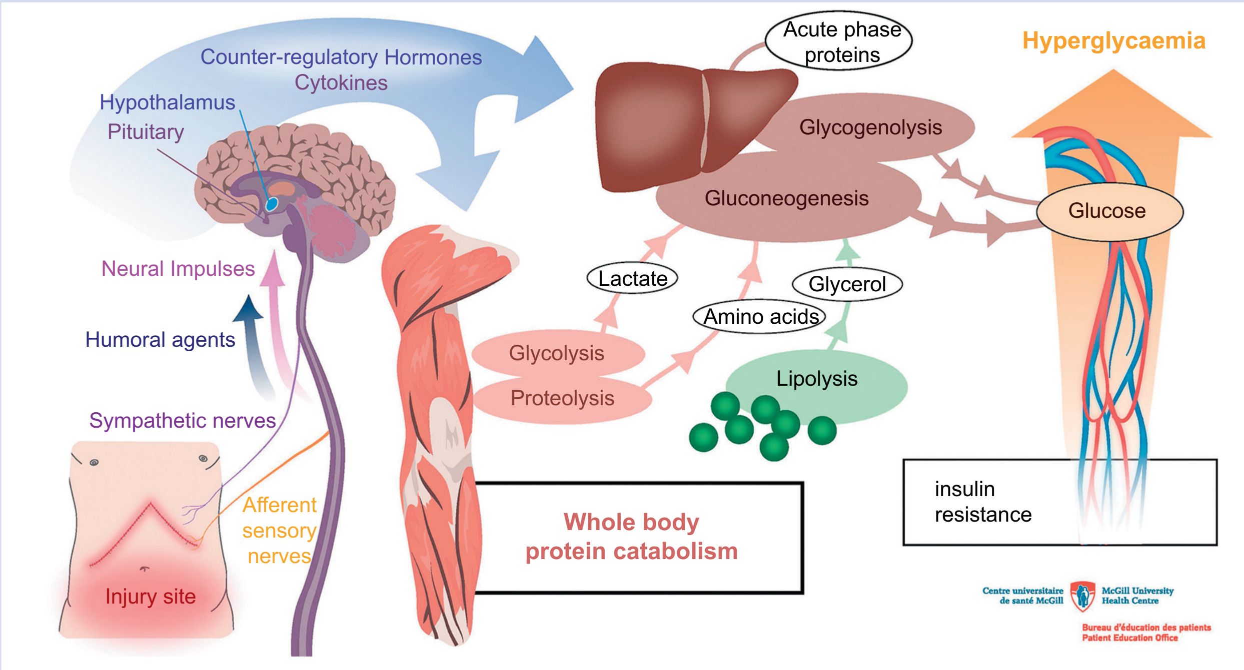

Fig 1. Surgical stress response. An increase in circulating glucocorticoids, catecholamines, and glucagon (i.e. counter-regulatory hormones) is elicited by activation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system. The response is mediated by afferent nerves and humoral factors including cytokines generated from the site of injury. Mobilisation of energy reserves promotes hyperglycaemia and catabolism. Hyperglycaemia develops as a consequence of insulin resistance coupled with an inappropriately high hepatic glucose production. Proteolysis and lipolysis accelerate to provide precursors for gluconeogenesis. The resultant amino acid efflux also supports the synthesis of proteins involved in the acute-phase response. (Reprinted with permission from Gillis et al[5], figure 1.)

Quality of surgical and perioperative care

Traditional surgical care includes unnecessary elements that amplify the surgical stress response[9] – that is, some traditional elements generate more stress than is required to achieve homeostasis. Fasting the night before surgery is one such example. Overnight fasting acts as a stressor, exaggerating the body's efforts to return to homeostasis and augmenting the catabolic response to surgery.[10] Fasting before anaesthesia was first proposed in the 19th century after several reports of death from pulmonary aspiration after operations performed under chloroform anaesthesia: a woman[11] had a toenail removed and a soldier[12] vomited during surgery of a gunshot wound to the thigh. Although international standards for anaesthesia[13,14] now endorse the consumption of food for up to 6 h and clear liquids for up to 2 h before elective surgery, many institutions continue to implement traditional fasting practices.[15]

Kehlet and colleagues[16] proposed a multimodal approach to improve recovery after surgery. This approach was later broadened by the ERAS Study Group,[17] which led to structured evidence-based perioperative protocols, as published by the ERAS Society[18] and other groups such as Society of American Gastrointestinal and Endoscopic Surgeons (SAGES),[19] to replace unnecessary traditional surgical care elements with evidence-based elements that attenuate the negative aspects of the surgical stress response.

ERAS protocols consist of multimodal, multidisciplinary perioperative elements that can improve outcomes.[18,20] Many ERAS care elements, such as the use of minimally invasive surgical techniques and avoiding fasting, minimise the stress response to surgery and help maintain homeostasis,[9] so that the patient avoids serious catabolism and consequent losses of body protein,[21] strength,[22] and function.[23] The safety and efficacy of using ERAS protocols in colorectal surgery have been observed in single-centre cohort studies,[24] multinational multicentre trials,[25] and in several meta-analyses of RCTs.[26,27] Many studies have demonstrated that ERAS care for colorectal surgery and for major abdominal surgery[28] reduced length of stay,[27–29] complications,[27–29] and costs.[29] Nevertheless, it should be noted that the evidence base for ERAS includes some studies of low quality, small sample sizes, or both, and studies of high risk of bias (e.g. inadequate description of attrition and absence of blinding).[30] Furthermore, some studies that are labelled as 'ERAS' have not implemented all ERAS elements or reported their elemental adherence.[18]

The observed clinical improvements in many sites using ERAS care can largely be traced back to the implementation of a standardised, evidence-based perioperative care pathway[31] that reduces physiological stress and attenuates catabolic perturbations in metabolism.[32,33] The ERAS elements, however, have historically focused on the immediate perioperative period, and there is more to be gained if all *preoperative* modifiable patient-related factors are optimised before surgery. A recent review of 13 published ERAS guidelines identified that only five of these guidelines recommended prehabilitation (with strength of the recommendation ranging from strong to moderate).[34] With this remaining review, we

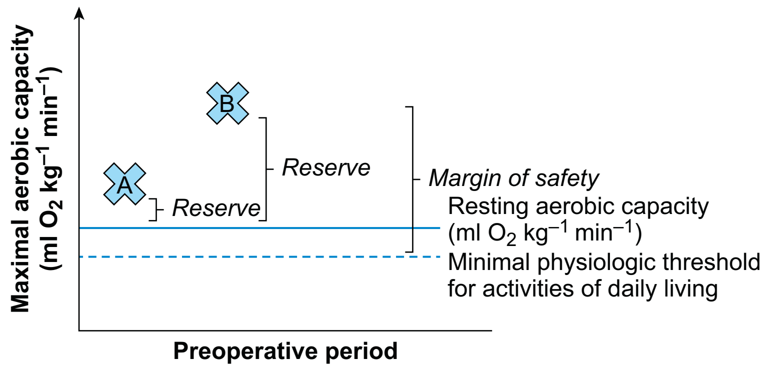

Fig 2. Cardiopulmonary reserve and exercise capacity. Hypothetical patients (patients A and B) participate in cardiopulmonary exercise testing before surgery. Patient A exhibits poor exercise capacity, has little cardiorespiratory reserve (resting − maximal), and is perilously close to the minimal physiological threshold required for functional independence. For this patient, a decompensating event as simple as bed rest after surgery could threaten functional independence. Patient B has excellent exercise capacity and cardiorespiratory reserve, contributing to a margin of safety that would likely permit this patient to withstand surgical stress without compromising functional independence. Ideally, patient A would improve their cardiorespiratory status before surgery, to be similar to patient B, and thus be a better candidate for surgery who is more likely to experience an uneventful postoperative course (described further in section 'Prehabilitation and functional capacity').

offer our perspectives on how the preoperative condition of the patient and prehabilitation prepare the patient for surgical stress and promote earlier return to homeostasis. We also offer future research suggestions so that these assumptions can be adequately tested.

Preoperative condition of the patient

Despite the implementation of ERAS care, complications after colorectal surgery can remain as high as 45%,[29] and most patients do not return to their baseline level of function even 8 weeks after surgery.[35] These poor patient outcomes might be the result of unchecked preoperative patient-related factors.[36,37] Individual patient characteristics can influence the natural response to surgical injury, such that the response is impaired, exaggerated, or prolonged, and thus more likely to produce adverse outcomes.[7] The following section will detail how the preoperative condition of the patient influences postoperative outcomes.

Cardiopulmonary reserve and exercise capacity

Major surgery increases oxygen consumption by as much as 50% to meet a heightened global oxygen demand, including the elevated post-surgical metabolic needs of the liver and muscle.[38] The cardiorespiratory system must function to meet this additional oxygen demand, and the inability to increase cardiac output to meet systemic oxygen requirements is thought to be one potential cause for a range of serious postoperative complications, including myocardial infarction.[39–41] A compromised systemic blood supply is also linked to surgical site infections (e.g. neutrophils, which are part of primary defence, must migrate to the wound),[42] and the failure to oxygenate gut tissues is a hypothesised culprit in the development of anastomotic leakages after colorectal surgery.[43] It is for this reason that the assessment of adequate cardiorespiratory performance has long been used to identify high-risk patients requiring modified perioperative management.[40]

Cardiopulmonary exercise testing provides an objective measure of cardiorespiratory performance under conditions of stress through the measurement of oxygen uptake at increasing levels of physical work (i.e. exercise capacity).[44] Poor exercise capacity (also referred to as exercise intolerance or the inability to perform physical exercise as expected[45]) can be the result of inadequate cardiac reserve, myocardial ischaemia, age- or disease-related deconditioning, and/or poor pulmonary reserve.[46] Before surgery, poor exercise capacity is suggestive of a future inability to increase cardiac output to meet elevated post-surgical oxygen demands.[40] The 2018 METS (Measurement of Exercise Tolerance before Surgery) trial used cardiopulmonary exercise testing to measure peak oxygen consumption in 1400 patients scheduled for elective noncardiac surgery, and found that a lower peak oxygen consumption predicted moderate–severe postoperative complications during hospitalisation.[47] Before surgery, these patients demonstrated poor ability of their cardiorespiratory system to delivery oxygen under stress.[40]

Cardiorespiratory performance contributes to a *physiological capacity* – defined as the capacity for organs and biological systems to function under stress.[48] A minimum physiological threshold is required to independently conduct daily tasks (i.e. activities of daily living) and to perform physical exercise.[49,50] For a patient with poor preoperative cardiorespiratory/exercise capacity, the physiological challenge of surgery can easily surpass their physiological threshold and compromise their functional independence. In fact, the development of functional impairments and iatrogenic disability – referred to as 'hospitalisation associated disability'[51] – are not uncommon occurrences in older adults who have had surgery[52] or require hospitalisation.[53] The preoperative condition of the patient, surgical stress elicited, and post-surgical immobility (associated with traditional models of surgical care)[53] all contribute to this phenomenon.[54] Assessment of cardiorespiratory performance is thus an important preoperative consideration to identify those who are at risk of surgical complications and those who are at risk of postoperative functional decline.

Altogether, without adequate cardiorespiratory capacity to sustain the physiological response to stress, a patient might not be able to meet the added demands of surgery and could experience poor surgical outcomes as a result. Exercise capacity thus represents a margin of safety that is not only protective against the development of postoperative complications, but also provides protection against the development of future functional impairments (Fig. 2). Values of exercise capacity derived from cardiopulmonary exercise testing[44] have been demonstrated to predict all-cause postoperative mortality,[55] prolonged hospital stay,[56] and survival after major surgery.[57,58] Comparably, preoperative functional impairment[59] or slow walking speed before elective colorectal,[35,36,60] cardiac,[61] and noncardiac major surgery[62] have been found to be associated with higher postoperative morbidity and prolonged recovery of baseline function.[59,63,64]

Energy reserve and metabolic capacity

The physiological response to surgical injury includes catabolism of energy/nutrient reserves (glycogen, body protein, and fat mass) to sustain energy production and to provide substrates for the healing processes involved in convalescence (e.g. synthesis of acute phase proteins).[5] A patient with poor energy and nutrient reserves before surgery – as a result of malnutrition, sarcopaenia, or both – compromises reserves to support this stress-induced mobilisation of substrates.[65] In addition, poor energy reserves contribute to a *low physiological reserve* (as seen in frailty) and this physiological deficit influences a patient's ability to mount a 'typical' stress response to cope with the surgical stress elicited.[66] As such, the physiological response to surgery both negatively affects patients with low preoperative reserve and is also affected by patients' reserve status.

A patient with adequate *physiological reserve* is believed to have the *physiological capacity* to endure stress and return to normal structure and function within a relatively short period of recovery (Supplementary Table S1). At the cellular level, adequate physiological reserve might be represented as excess metabolic capacity[67] – that is, the ability to readily exceed normal basal metabolic function when needed to meet heightened metabolic demands. Decline or exhaustion (e.g. from disease, illness, and/or age) of the excess capacity of biochemical structures (e.g. mitochondria[68]) and metabolic pathways (e.g. glucose utilisation in muscle cells[69]) might contribute to diminished physiological reserve, and thus diminished physiological capacity of organs and biological systems to function under stress.[67]

Importantly, although we might refer to body protein as a 'reserve,' this is not strictly correct. Stored glucose (glycogen) and excess body fat represent true energy reserves. Body protein, however, including somatic and visceral proteins, serve a specific function. Catabolism of body protein can thus limit function.[70] Patients with depleted body protein have less 'reserve' to sacrifice to the cause of injury without serious concomitant losses in postoperative function.[8,71] As a result, patients with sarcopaenia might be more susceptible to the negative consequences of postoperative catabolism, which include physiological losses and functioning of skeletal, respiratory, and gut tissues.[72,73] Clinically, these losses might be represented as reduced strength,[74] impaired ability to cough after surgery (increasing susceptibility to respiratory infections), and impaired gut mucosal barrier (increasing susceptibility to infections[75]). Having adequate skeletal muscle tissue to participate in postoperative whole-body protein metabolism permits flexibility to rapidly respond to challenges while maintaining essential functions.[186]

Another patient group that presents to surgery with poor physiological reserve and function are patients with malnutrition.[76] Patients with colorectal cancer awaiting surgical resection, for instance, exhibit progressively worse functional walking capacity with each level of worsening nutritional status.[76] Nutrition deprivation depletes energy/nutrient reserves, and a chronically deficient supply of nutrients deprives the body of the essential substrates required to fuel normal metabolic function.[77] In order to survive, the body adapts, making cellular and hormonal adjustments, including reduction of the basal metabolic rate, which, collectively, reduces function but slows deterioration.[7,78,185] The impaired physiological effects associated with malnutrition are often represented as a blunted inflammatory response to injury[7,79] and immune incompetence.[80] A failure to activate necessary inflammatory and immune responses to establish early homeostasis in response to stress might contribute to the observed vulnerability of malnourished patients to experience adverse events after surgery, including greater odds of developing a complication from surgery,[81–85] more frequent readmissions to hospital after surgery,[82,86–88] longer hospital stays,[81,82,85–87] and greater risk of mortality.[82,87,89,90]

Deficient energy reserves and reduced metabolic capacity, as seen in malnutrition and sarcopaenia, culminate in the form of frailty. Although there is no single accepted definition of frailty,[91,92] the definition provided by Campbell and Buchner[93] is comprehensive: 'a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure. As a consequence, the frail person is at increased risk of disability and death from minor external stresses'. Frail patients are believed to have reduced physiological reserve, and thus reduced physiological capabilities *across multiple organ systems*, which ultimately reduces the natural complexity of their biologic systems.[94] A stress response necessitates dynamic coordinated actions and adaptation within and across several complex physiological systems to restore homeostasis. As a result, the compensatory mechanisms attempting to establish homeostasis in a frail patient might fail. A frail patient, for instance, might respond to injury with impaired action (limited in responsiveness, strength, range) to fight infection or impaired ability to maintain tissue perfusion within acceptable limits.[66] Equally possible, a frail patient might experience prolonged or exaggerated stress response owing to dysregulated signalling pathways involved in homeostatic control.[94] For instance in a recent prospective observational mechanistic study of microRNAs (a proposed biomarker of acute coronary syndrome) after noncardiac surgery, bioinformatic analysis of differentially expressed microRNAs suggested that an aberrant inflammatory response, commonly observed in patients with pre-existing or acquired loss of cardioprotective signalling mechanisms (e.g. older adults), was associated with myocardial injury.[95] Several studies have

Table 1 An example of a multimodal prehabilitation program. Prehabilitation programs are evolving as ongoing trials add to our understanding of who, what, and how patients benefit from prehabilitation.

	Prehabilitation components		
	Nutrition	**Exercise**	**Psychosocial**
Screen and assess	Canadian Nutrition Screening Tool[104] Patient-Generated Subjective Global Assessment (PG-SGA)[105] Haemoglobin A1C Body composition[106] C-reactive protein[106]	Duke Activity Status Index[108] Gait speed[109] Six-minute walk test (6MWT)	Hospital anxiety and depression scale (HADS)[110] Distress thermometer[111]
Diagnose or identify	Malnutrition Sarcopaenia Poor glycaemic control Inadequate energy protein intake	Frailty Sedentary behaviour	Distress
Intervene	Risk stratified and personalised[107]: PG-SGA <4 or SGA A: Nutrition class PG-SGA 4–8 or SGA B: Short, targeted intervention to treat primary diagnosis PG-SGA ≥9 or SGA C: Specialist intervention with one-on-one counselling (often requires supplementation or nutrition support).	Risk stratified and personalised to include major muscle group strengthening and aerobic prescription.	Personalised interventions for patients and caregivers can include: Breathing exercises Visualisation Relaxation Guided meditation Goal setting and self-monitoring Positive reinforcement Social support
Monitor and evaluate	PG-SGA numeric score Food records and recalls Adherence to supplements Weight Body composition	Borg rating of perceived exertion scale to monitor progression 6MWT 30-s sit-to-stand Arm curl test Accelerometer Activity logs or questionnaires	HADS HeartMath Patient reported outcomes, experience, and satisfaction questionnaires

identified that frailty is an independent risk factor for serious postoperative complications,[96–98] mortality,[96,98] prolonged length of hospital stay,[96] and institutional discharge.[97,99]

Putting this together, the degree of surgical stress elicited influences surgical outcomes and timing of recovery. Whether the magnitude of surgical stress elicited is ‘critical’ is dependent, in part, on the patient and their unique physiological reserve and physiological capacity. The relationship between physiological reserve capacity and surgical stress is represented in Supplementary Figure S1. A patient with adequate physiological reserve and physiological capacity can draw upon these reserves during times of stress (e.g. exercise, surgery), which should enable adequate functioning of organs and biologic systems to restore homeostasis. As an example, an older adult with adequate *reserve* and thus excess metabolic *capacity* can *function* to generate adenosine triphosphate (ATP) for muscle contraction in response to the physiological stress of lifting groceries. In contrast, a patient with low physiological reserve might not be able to extend metabolic capacity to cope with the metabolic challenge of a stressor. As an example, a sarcopenic cancer patient with atrophied cardiac muscle[100] (i.e. reserve) has reduced cardiomyocytes for production of ATP (i.e. reserve capacity), which could impact the contractile function needed to maintain tissue perfusion in response to the workload of surgical stress.[101] Physiological reserve capacity is thus believed to represent a potentially modifiable margin of safety that protects the patient from deteriorating beyond their theshold of physiological integrity to maintain their functional independence in response to a physiological challenge.

Prehabilitation and functional capacity

The physiological response generated by surgical injury is a predictable impending burden awaiting surgical patients. Prehabilitation programs aim to prepare patients physically and emotionally to withstand the stress of surgery.[102] Although there is no single definition for prehabilitation and these programs vary,[103] the focus of this review is on multimodal prehabilitation programs, including nutrition, exercise, and psychological strategies that aim to enhance functional capacity before surgery and facilitate earlier return of functional capacity after surgery (see Table 1 for an example of a multimodal prehabilitation program[102,104–111]). Maintaining function is considered the most important target by both clinicians[112] and patients.[113] The following section provides evidence that supports the use of preoperative interventions to modify physiological reserve, enhance functional capacity, and mitigate poor surgical outcomes.

Functional capacity

Functional capacity is the most commonly measured outcome in prehabilitation research.[114] Functional capacity is the ability to perform and cope with activities of daily living, which requires an integrated effort of the cardiovascular, pulmonary, and skeletal muscular systems.[115] A minimal physiological capacity is required for unimpaired physiological reserve,[49] which is influenced by exercise,[116] nutritional,[117] and cognitive/psychological[118] reserve statuses, in a reciprocal-type relationship. As an example, functional capacity is affected by mental wellness, and also contributes to mental well-being.[119,120]

Therefore, the definition of functional capacity is all encompassing and recognises the interconnectedness among physical, psychological, and nutritional (metabolic) statuses.

Physical status

The exercise component of multimodal prehabilitation aims to enhance physiological reserve and functional capacity of the cardiorespiratory (i.e. exercise capacity) and musculoskeletal (i.e. strength, body protein) systems.[121] Habitual physical activity and exercise are well known to preserve physiological reserve[122] and to build functional capacity.[123,124] Several prospective studies have identified that exercise training can be carried out successfully in the waiting period before surgery to improve functional capacity.[125,126] In small, non-randomised[126] and randomised[127] studies of patients with advanced rectal cancer, 6[126] and 9[127] week structured exercise training programs significantly improved exercise capacity, measured with cardiopulmonary exercise testing, post-neoadjuvant therapy and before surgery. In addition, some (but not all[128,129]) meta-analyses have identified positive outcomes when exercise interventions were applied as part of a multimodal intervention before surgery.[130] A recent meta-analysis of eight RCTs among 422 major abdominal surgery patients found that preoperative interventions that included physical exercise produced a protective effect against postoperative morbidity, and, in particular, pulmonary complications as compared with standard care.[130] Finally, a recent umbrella review of 55 systematic reviews of cancer prehabilitation identified there was low to very low certainty evidence that exercise prehabilitation reduces the risk of complications, non-home discharge, and length of stay.[187]

In addition, exercise improves metabolic flexibility, defined as the ability to adapt metabolism (e.g. substrate use and storage), in response to available substrates and requirements.[131] Exercise training is believed to improve exercise performance, in part, through enhanced capacity of skeletal muscle to oxidise both fatty acids and glucose to fuel performance (i.e. metabolic flexibility).[132] Before surgery, it is not uncommon for patients without a history of diabetes to present with insulin resistance and a disturbed glucose metabolism that abnormally raises blood glucose concentration[133,134] and is representative of a metabolically *inflexible state*. In a cohort of 120 patients who had colorectal cancer without known diabetes, one in four presented with an elevated preoperative haemoglobin A1c (an indication of average blood glucose over the preceding few months), which was associated with higher postoperative glucose levels and an increased odds of developing a complication.[133] Several other studies have found that preoperative hyperglycaemia and insulin resistance are associated with serious postoperative complications[134–136] and 30-day mortality.[137] Being in a metabolically flexible state before surgery is likely to benefit patients by supporting the ability to respond to stress with an adaptive metabolic response that efficiently restores/maintains energy homeostasis without serious consequent losses of body protein. In fact, a stable isotope study identified that whole-body protein catabolism on the second day after colorectal cancer surgery was 50% greater in patients with diabetes compared with patients without diabetes.[138]

Nutritional status

The nutrition component of multimodal prehabilitation primarily serves to prevent and treat malnutrition.[139] Preoperative identification and treatment of nutritional deficits have long been known to improve surgical outcomes.[72] A meta-analysis of 15 RCTs, including 3831 malnourished patients undergoing a variety of surgical procedures, identified that perioperative nutritional support effectively decreased the incidence of complications and reduced length of hospital stay by approximately 2 days.[140] Given that surgical patients have plenty of ‘opportunity’ to develop malnutrition throughout the perioperative period,[139] pre-emptive nutrition strategies may also be of value.[141] As an example, cancer patients without any obvious signs of malnutrition randomised to 14 days of preoperative oral nutrition supplementation, *vs* standard of care, suffered significantly fewer minor and serious complications.[142] Interestingly, as the patients awaited surgery, a decline in both serum albumin and total lymphocyte count was observed in the control group but not in the intervention group.[142] These findings suggest that preoperative nutritional support can exert a positive effect, in part, through maintenance of nutritional status and physiological function. Several prospective studies corroborate these results.[80,143] In a study of malnourished patients with and without inflammatory bowel disease, mitochondrial complex I activity measured in peripheral blood mononuclear cells (immune cells: lymphocytes, dendritic cells, and monocytes) were lower in malnourished individuals (independent of disease) as compared with age-matched healthy controls.[80] Providing nutritional support (enteral, parenteral, oral nutrition supplements) for 1 week increased complex I activity significantly in malnourished patients,[80] and activity returned to normal after 1 month of nutrition support.[144] Additionally, a recent umbrella review of 55 systematic reviews of cancer prehabilitation identified there was low to very low certainty evidence that nutrition prehabilitation reduces risk of complications, mortality, and length of stay.[187]

The secondary aim of multimodal nutrition prehabilitation is to augment exercise gains (exercise capacity, body protein, strength) to enhance physiological reserve and functional capacity.[139] Provision of key anabolic nutrients, including dietary protein, support anabolic gains.[145] Dietary protein supplies amino acids, which serve as the building blocks for body protein (i.e. ‘reserve’).[146] Although there is evidence of reduced anabolic capacity in patients with advanced cancer, a substantive dose of amino acids has been found to overcome anabolic failure and stimulate protein anabolism in this group.[145,147] Although dietary protein supplies amino acids (i.e. substrate), several micronutrients (vitamins, minerals) are essential components of energy and protein metabolism.[146] Pyridoxine (vitamin B_6, abundant in animal products) for instance is a coenzyme involved in nitrogen transfer between amino acids and thus plays a role in protein building and breakdown.[146] A micronutrient deficiency could potentially inhibit anabolic potential of the dietary protein consumed and thus serves as an additional rationale for nutrition provision/correction of malnutrition.[186]

Psychosocial status

Most patients experience psychological stress before surgery.[148] Some observational evidence suggests that severe psychological distress, as seen in anxiety or depression, can produce a dysregulated hypothalamic–pituitary–adrenal axis response, initiating a stress response *before surgery* and contributing to postoperative disruptions in immune function.[149] Indeed, preoperative anxiety, depression, fear, and psychological stress are associated with worse surgical outcomes, including length of

Table 2 Summary of our experience with the prehabilitation components and their effect on functional walking capacity before colorectal surgery for cancer. *Note that adherence to the prehabilitation program and sample sizes were not equal in these studies, which may have influenced the findings of an improvement in function before surgery. The ability to adhere to both individual prehabilitation components and multi-components before surgery needs to be investigated.

Studies	Proportion of patients that experienced a clinically important improvement in functional walking capacity before surgery (measured with the 6-min walking test)	Potential mechanism for observed improvement*
Exercise prehabilitation, RCT	33%	• Enhance substrate utilisation/metabolic flexibility • Enhance cardiorespiratory capacity
Nutrition prehabilitation, RCT	50%	• Provide substrate to correct deficiencies and augment physiological reserve
Multimodal prehabilitation, RCT	53%	• Provide substrate to correct deficiencies and augment physiological reserve • Enhance substrate utilisation/metabolic flexibility • Enhance cardiorespiratory capacity
Multimodal prehabilitation in patients with low functional capacity at baseline (pooled, retrospective analysis)	72%	• Patients with greatest functional deficits, attain greatest functional benefits from participating in prehabilitation

References: Exercise only PMID: 20602503; nutrition only PMID: 26208743; multimodal is reference 162 or PMID: 25076007; low functional capacity: PMID: 27476586.

hospital stay.[150,151] Additional explanations for these poor outcomes include that depressed patients have been found to be less physically active before surgery, with resultant lower functional capacity,[152] and anxious patients have been found to require more anaesthesia than less distressed patients[153,154] (which could augment opioid-related side-effects, including nausea,[150] that delay hospital discharge).

The psychological component of prehabilitation interventions aim to support behaviour change (i.e. reinforce exercise and nutrition interventions) and promote mental wellness before surgery;[151] newer studies have aimed to reduce postoperative delirium as well.[155] Qualitative patient-partnered studies in colorectal surgery suggest that explaining the rationale for interventions and the inclusion of caregivers is an important component of establishing the necessary patient buy-in to support behaviour change.[148,156] In addition, receipt of emotional support from the prehabilitation team was identified by interviewed patients as a top priority for prehabilitative services.[148] Many prehabilitation programs strive to support agency and self-efficacy by engaging patients early in the recovery process and by providing patients with tools, such as deep breathing, to cope with psychological stress and promote resilience.[151,157] A meta-analysis of prospective preoperative psychological interventions – including relaxation techniques, guided imagery, stress management, and psychotherapeutic interventions – in 605 cancer patients implemented 1–2 weeks before surgery identified that patient-reported outcomes before and after surgery were enhanced with psychological prehabilitation.[158] A recent Cochrane review of RCTs of adult participants undergoing elective surgery (n=10 302) reported there was low-quality evidence that psychological preparation techniques (including provision of procedural information, behavioural instruction, and cognitive interventions) were associated with lower postoperative pain, length of stay, and negative affect (such as anxiety, depression) compared with controls.[159] Furthermore, multimodal prehabilitation has been found to improve functional walking capacity among depressed patients before colorectal cancer surgery.[152]

In summary, preoperative patient characteristics manifest differential capacities to respond to stress and to recover from injury. Prehabilitation interventions aim to enhance recovery by targeting preoperative patient characteristics to augment physiological reserve and capacity (Table 2).

Proposing an integrated hypothesis of ERAS with prehabilitation

Several meta-analyses[130,141] and randomised trials[160–162] on uni-[127] and multimodal[162] prehabilitation have reported both clinical and functional benefits; yet, only a few studies have identified clinical benefits with the use of prehabilitation in an ERAS setting.[160,163] It is, however, difficult to understand the contribution of prehabilitation within studies conducted under ERAS care because very few studies have reported their adherence rate to the ERAS elements.[18,164] Given that ERAS care attenuates surgical stress and independently improves clinical outcomes (see section on *Quality of surgical care*), it might not be possible to further enhance clinical outcomes with prehabilitation at a site with high compliance to ERAS elements. Ample evidence, however, suggests that prehabilitated patients exhibit *resilience* under ERAS care.[35,162,165,166] Surgical resilience can be defined as the time it takes to return to homeostasis after surgery.[167] A retrospective analysis of pooled individual patient data from prehabilitation trials in colorectal cancer surgery identified that ERAS patients who participated in multimodal prehabilitation preserved their fat-free mass at both 4 and 8 weeks after surgery, compared with ERAS patients who received rehabilitation.[165] This is an anabolic benefit that has not been observed at other sites using ERAS care without prehabilitation.[21,35] A study following the outcomes of an institutional change in surgical practice from traditional to ERAS care, observed that

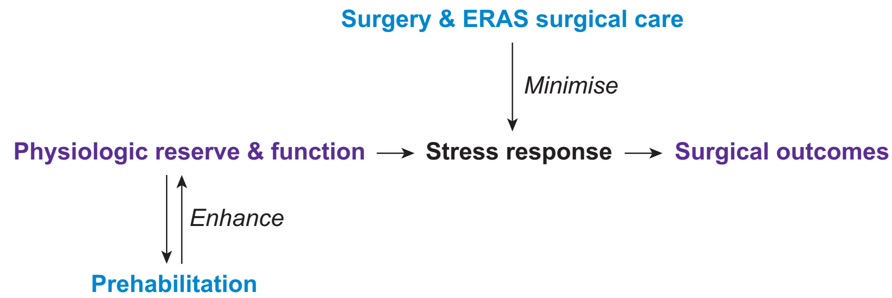

Fig 3. Perioperative interventions modify surgical outcomes through mediation of the surgical stress response. Patients present to surgery with unique *physiological reserves* and *physiological capacities* that influence *surgical outcomes*. A patient's physiological reserve can alter (i.e. mediate) *surgical stress*: a patient with adequate physiological reserve will likely generate a typical surgical stress response, whereas a patient with inadequate physiological reserve is likely to generate an impaired stress response (overexpressed or underexpressed responses to injury). Enhanced recovery after surgery (ERAS) and prehabilitation interventions can modify surgical outcomes in complementary ways through mediation of the surgical stress response. ERAS interventions minimise the surgical stress response, whereas prehabilitation interventions enhance physiological reserve and functional capacity. Having poor physiological reserve and functional capacity (e.g. malnutrition, frailty) can make full participation and adherence to prehabilitation challenging, potentially limiting the intervention's efficacy.

patients after ERAS maintained fat-free mass 8 days after surgery compared with patients receiving traditional surgical care, but did not maintain these gains at 28 days after surgery.[21] In addition, a prospective study in patients with colorectal cancer indicated that *twice as many* prehabilitated patients recovered their functional walking capacity, as defined by the 6-min walk test (6MWT; a practical measure of functional capacity), at 8 weeks after surgery compared with the patients who received ERAS care alone.[35] These findings suggest that prehabilitated patients are more resilient, with a superior return to normal body structure and function, even within the context of modern surgical care practices of ERAS.

Based on review and synthesis of the evidence, the following hypothesis is proposed to describe the underlying process by which individual patient-related factors might influence surgical outcomes: the patient's preoperative status modifies surgical outcomes through mediation of the surgical stress response (Fig. 3). ERAS is an intervention that modifies surgical outcomes through attenuation (mediation) of the stress response. Prehabilitation, is complementary to ERAS, because it modifies surgical outcomes by targeting preoperative physiological reserve capacity, which in turn affects the stress response and outcomes.

However, it is important to note that individual patient characteristics can also influence the efficacy of prehabilitation interventions. For instance, a pooled analysis of malnourished patients with colorectal cancer suggested that these patients suffer from low functional capacity before surgery as compared with their well-nourished counterparts,[76] and the odds of improving functional capacity with prehabilitation were low.[168] These negative findings could in part be related to the malnourished patients' comparatively lower adherence to the exercise program (mean adherence: 84% *vs* 71%[168]). Similar findings were reported in prehabilitated frail patients: mean adherence to supervised exercise sessions was only 68%, and outcomes were similar in both the intervention and control groups.[163] These findings suggest that although prehabilitation has the potential to enhance physiological reserve and functional capacity to promote early recovery, individual patient characteristics can make adequate prehabilitation participation challenging.

Table 3 Phases with impact on surgical recovery.

Phase of recovery	Definition	Time frame	Example measures
Pre-admission (proposed)	Preparation for postoperative recovery	Weeks to months	Adequate functional capacity to withstand surgical stress; resolution of malnutrition; sense of control and self-efficacy; prophylactic measures provided such as antibiotics and carbohydrate loading
Intraoperative	During the course of the surgical procedure	Hours	Fluid balance, pain and anaesthesia management
Postoperative			
Early	Until discharge from PACU	Hours	Vital signs
Intermediate	Until discharge from hospital	Days	Bowel recovery; length of hospital stay
Late	Until illness no longer disrupts everyday life	Weeks to months	Patient-reported resolution of symptoms; return to pre-surgery activities and functional capacity

Future research directions and considerations

'Postoperative recovery' is a commonly used but poorly defined concept.[169] Indeed, a single definition for postoperative recovery may not be appropriate: surgical recovery is a complex process involving multiple domains – physical, physiological, psychological, social, economic – all with different time frames of restoration.[172] In recent years the Standardised Endpoints in Perioperative Medicine (StEP) initiative has reached consensus on the use of many important recovery outcomes, including cardiovascular and patient-oriented outcomes.[170,171] However, definitions of postoperative recovery do not commonly include the impact and role of the preoperative phase. A growing body of literature suggests that postoperative *recovery is not a passive process and begins preoperatively*. For instance literature on preoperative risk calculators/tools,[173] preoperative interventions,[162] and surgical resiliency[174] all suggest that key indicators of recovery (or delayed recovery) can be identified and optimised before surgery. For ERAS and other surgical research studies measuring recovery, we suggest that the preparation for recovery or the 'pre-surgery recovery phase' needs to be included. Table 3, adapted from Lee and colleagues,[172] describes the phases (with the pre-surgery phase added) that have direct impact on surgical recovery. By adequately preparing patients for surgery, patients are better candidates for surgery, and, as a result, are likely to recover well from surgery.

Carli and Mayo[175] proposed the following guidelines to measure and evaluate postoperative recovery: (1) it should be biologically plausible for the exposure/intervention to influence the outcome; (2) both the outcome and exposure/intervention should be measured accurately; (3) consider the statistical and clinical implications of performing the measurements/instruments; and (4) external variables that influence the outcome–exposure/intervention relationship should be identified and accurately measured. These guidelines provide a good framework to continue researching our global hypothesis: the patient's preoperative status modifies surgical outcomes through mediating the surgical stress response; and, that prehabilitation modifies surgical outcomes by enhancing the patient's preoperative condition (physiological reserve and function). The following points are proposed as next steps to advance research in prehabilitation and test these hypotheses:

1. *It should be biologically plausible for the exposure/intervention to influence the outcome*. Mechanistic studies should be conducted to evaluate the influence of preoperative characteristics on the surgical stress response. Many of the empirical studies that elucidated the response to surgical stress were conducted long ago and not completed under modern ERAS practices. Knowledge of the stress response should be the foundation by which surgical interventions, such as prehabilitation, are based. By repeating these pivotal studies today, we could answer the following questions: Which preoperative characteristics *under ERAS care* impair the surgical stress response? Can we predict the direction of surgical stress response dysfunction (overexpressed or underexpressed) based on preoperative surgical characteristics?
2. *Relevant outcomes should be measured*. The 6MWT is often used as the primary outcome in prehabilitation research. However, this is a measure of functional walking capacity and might not be sensitive to early changes in physiological reserve capacity.[50] A physiological improvement is likely to confer benefits even if it has not yet translated into an obvious functional improvement. In fact, improvements in physiologic function likely precede clinical presentation[94]; thus, additional measurements of physiological reserve and function (e.g. phase angle, blood pressure variability) should be considered in future trials to evaluate whether prehabilitation was successful. A core outcome set could greatly advance the prehabilitation literature.
3. *The intervention should be fully described and its completeness of implementation reported*. Few studies have measured prehabilitation interventions well. A recent scoping review of 37 nutrition-focused prehabilitation-labelled studies in oncology identified that one-quarter of these studies included a nutrition intervention of which the specific components were indiscernible, and two-thirds of these studies did not monitor the intervention.[114] How do we know if the prehabilitation intervention itself was successful if the intervention was not measured accurately? Proctor and colleagues[176] proposed the following equation to conceptualise implementation success:

   $$\text{Implementation success } (I) = f_E + \text{IOs}$$

   where f_E is the effectiveness of the treatment being implemented and IOs denotes implementation details.

   When an intervention fails to deliver, it is critical that we are able to attribute failure to either the intervention itself (f_E) or the factors associated with its implementation (IOs), or a combination of the two. Prehabilitation-specific reporting guidelines/checklist could greatly advance the literature.[176]
4. *Consider the statistical and clinical implications of the measurements/instruments*. Bowyer and Royse[177] proposed that an ideal measure of recovery would 'determine whether the process of recovery has progressed to an acceptable threshold (dichotomous analysis) and then determine how much beyond the minimum threshold recovery has progressed (continuous analysis)'. An ideal outcome measure might be continuous, harnessing statistical power, but could also be dichotomised, for instance, by the minimal clinically important difference (MCID), permitting rich data analysis and conclusions. Although the MCID for the 6MWT has been established to be 19 m for colorectal surgery,[64,178] we do not know the MCID for other physical function measures, such as strength and balance, which, altogether with 6MWT, might be more representative of a change in the patient's overall preoperative condition and recovery. Furthermore, is the established MCID for the 6MWT applicable in frail, malnourished, and sarcopenic patients?
5. *External variables that influence the outcome-exposure/intervention relationship should be identified and accurately measured*. Measurement and evaluation of extraneous, 'third' variables is an area of prehabilitation research in need of improvement. For instance, the results of published prehabilitation research are rarely stratified by preoperative characteristics, such as malnutrition, and examined separately before pooling. It is unlikely that all patient groups will respond to a prehabilitation intervention similarly, so examining the effects of prehabilitation on patient subgroups is vital.[164]

Finally, it should go without saying that primary studies should be designed to avoid or limit bias[179,180] (e.g. allocation concealment, blinding, handling of missing data) and that quality reporting should meet consensus standards (e.g. Consolidated Standards of Reporting Trials [CONSORT][181] or Strengthening the Reporting of Observational Studies in Epidemiology [STROBE][182]). Systematic reviews should be developed with consideration of AMSTAR-2[183] and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[184]

Conclusions

ERAS minimises the physiological response generated by surgical injury with standardised evidence-based perioperative care; yet the ERAS care elements focus mainly on the intra- and postoperative periods, which may not sufficiently enhance recovery if *preoperative* patient-related factors have not been modified before surgery. We propose that the process of surgical *recovery begins before* the *incision* and that preoperative patient characteristics mediate the surgical stress response and thus modify surgical outcomes. As examples, a patient with malnutrition may generate an impaired inflammatory response, making them more susceptible to infection, whereas a patient with sarcopaenia might have a lower threshold for what would be considered a 'critical' stress response in which the stress-induced degradation of body protein further depletes their compromised reserve and threatens their functional independence. Prehabilitation aims to augment physiological reserve and enhance functional capacity before surgery with nutritional, physical, and psychosocial strategies to prepare patients to withstand the surgical stress response. Integration of prehabilitation, which enhances tolerance to surgical stress, with ERAS care, which minimises surgical stress, promotes surgical resilience.

Authors' contributions

Conception and interpretation of this work: CG, OL, FC
Drafting of the manuscript: CG
Critical revisions of the manuscript: OL, FC
All authors approved the final version of the manuscript.

Declarations of interest

OL is a co-founder of the ERAS® Society, serves as its current chairman, and co-author of several of the guidelines from the ERAS® Society. He also held a patent for a preoperative carbohydrate drink until 2013, and has received honoraria for speaking, travel and advice unrelated to the current work from Fresenius-Kabi, Nutricia, BBraun, Advanced Medical Nutrition. CG has received honoraria for speaking and travel from Abbott Nutrition and Nestle which is unrelated to the current work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.12.007.

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