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Paradigm shift in gastrointestinal surgery – combating sarcopenia with prehabilitation: Multimodal review of clinical and scientific data

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Abstract

A growing body of evidence has demonstrated the prognostic significance of sarcopenia in surgical patients as an independent predictor of postoperative complications and outcomes. These included an increased risk of total complications, major complications, re-admissions, infections, severe infections, 30 d mortality, longer hospital stay and increased hospitalization expenditures. A program to enhance recovery after surgery was meant to address these complications; however, compliance to the program since its introduction has been less than ideal. Over the last decade, the concept of prehabilitation, or “pre-surgery rehabilitation”, has been discussed. The presurgical period represents a window of opportunity to boost and optimize the health of an individual, providing a compensatory “buffer” for the imminent reduction in physiological reserve post-surgery. Initial results have been promising. We review the literature to critically review the utility of prehabilitation, not just in the clinical realm, but also in the scientific realm, with a resource management point-of-view.

Key Words: Sarcopenia; Prehabilitation; Surgery; Frailty; Value; Gastrointestinal surgery

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Core Tip: The geriatric surgical population is rapidly growing and hence, clinicians

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have to take into account additional risk factors such as frailty. In particular, it is evident that sarcopenia is an independent predictive factor of postoperative outcomes. Prehabilitation represents a paradigm shift in geriatric surgical care, with the goal of enhancing functional capacity to withstand a forthcoming stressor. Emerging data has inspired healthcare professionals to not only adopt a multimodal approach, but also to pivot towards personalized programs.

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INTRODUCTION

A patient undergoing surgical procedure is subjected to a major stressor, and depending on the magnitude of the surgery, induction of the surgical stress response culminates in the derangements of metabolic processes and disruption of homeostasis [1]. Notwithstanding any surgical complications, major surgeries have been shown to reduce physiological and functional capacity of up to 40%. In addition, the subsequent inactivity and bed rest will induce rapid muscle atrophy, further resulting in muscle deterioration [2]. Hence, a fitter individual that can overcome the metabolic deconditioning will tend to recover faster and regain physical fitness back to baseline level. On the contrary, geriatric patients tend to have lower reserve, a mismatch to the physiological demand placed on the body, causing a delayed postoperative recovery. It is evident that increasing age is an important risk factor for postoperative adverse outcomes, such as prolonged length of stay (LOS), increased chance of complications, morbidity, and mortality [3-6]. The increased prevalence of postoperative comorbidities among elderly patients necessitates the implementation of preoperative regimes to mitigate such a phenomenon.

Frailty is a multifactorial phenomenon associated with aging that is characterized by an accelerated decline in physiological reserve and function across multiple organ systems of the body. A major component of frailty is sarcopenia, defined as the progressive loss of muscle mass and strength. It is also characterized by negative alterations in muscle architecture and poor muscle quality, concomitant with diminished regenerative capacity [7]. Not only does skeletal muscle coordinates contraction to enable locomotion, but also, from a metabolic angle, it regulates energy production, glucose uptake, and protein metabolism throughout the body [8,9]. Therefore, it is not surprising that skeletal muscle is one of the primary tissues mobilized to counteract the deficit in physiological reserve caused by the surgical stress response. It cannot be overemphasized that a patient must be physically fit to abate the physiological stressors to increase the probability of better surgical outcomes.

This is a review on the utility of prehabilitation to combat the effects on sarcopenia on surgical patients. We focused on the effects of sarcopenia on surgical outcomes, the rationale behind the increasing adoption of prehabilitation, and review the outcomes and cost effectiveness of such programs.

SARCOPENIA CORRELATES WITH ADVERSE SURGICAL OUTCOMES

A growing body of evidence has demonstrated the prognostic significance of sarcopenia in surgical patients and is an independent predictor of postoperative complications and outcomes. As attested by the numerous studies and reviews conducted, sarcopenia and its defining characteristics, such as low skeletal muscle mass, strength, and functional capacity, are associated with adverse outcomes. For example, a study demonstrated that patients with sarcopenia undergoing surgery for colorectal cancer had a higher incidence of postoperative complications, particularly infectious complications [10]. The study also highlighted that integrating functional

components of sarcopenia, such as muscle strength or physical performance, more accurately predicted postoperative complications. This was corroborated by another study in which sarcopenia was associated with more postoperative complications in sarcopenic patients with rectal cancer[11]. In addition, sarcopenia was shown to be a significant independent predictor of 1-year mortality in patients who had elective curative colorectal resection for cancer[12]. The sarcopenic group was significantly correlated with worse survival at 1 year, with an overall 1-year mortality of 15.6% compared to the non-sarcopenic group at 5.3%. Additionally, several meta-analyses conducted on patients undergoing gastrointestinal surgeries found similar results. In brief, a meta-analysis that included 11 cohort studies with 2419 participants demonstrated that sarcopenia was a high-risk factor for negative digestive carcinoma surgery outcomes[13]. These included an increased risk of total complications, major complications, re-admissions, infections, severe infections, 30-d mortality, longer hospital stays, and increased hospitalization expenditures. Similarly, another meta-analysis that included 11 studies with 4265 gastrointestinal surgery patients highlighted that sarcopenia was associated with an increase in late postoperative complications and the number of postoperative hospital readmissions[14]. Furthermore, a meta-analysis that interrogated seven observational cohort studies totaling 1440 patients, revealed a significant link between low muscle mass and mortality in patients undergoing abdominal aortic aneurysm repair[15]. Interestingly, one study demonstrated that detection of both preoperative sarcopenia and accelerated muscle loss after surgery in pancreatic cancer patients were associated with negative overall survival[16].

There are several studies documenting similar findings in patients undergoing cardiac surgeries. In a large single-center retrospective study involving 1119 patients that underwent heart valve surgery *via* median sternotomy, the sarcopenic group had significantly decreased long-term survival and increased major adverse cardiovascular events[17]. Similarly, out of 266 patients who underwent elective total arch replacement, 81 sarcopenic patients had a significantly worse 5-year survival, demonstrating that sarcopenia can be an additional risk factor to estimate the outcomes of thoracic aortic surgery[18]. In addition, lower psoas muscle area was associated with an increase in long-term mortality and in-hospital mortality or major morbidity in patients that underwent orthotopic heart transplantation[19]. Moving on to the respiratory system, a retrospective study consisting of 328 non-small-cell lung carcinoma (NSCLC) patients who underwent curative resection determined that sarcopenia was an independent unfavorable prognostic factor[20]. The sarcopenic group had a 5-year survival rate of 61% relative to 91% in non-sarcopenic group. Likewise, a meta-analysis involving 6 cohort studies consisting of 1213 patients with surgically treated NSCLC yielded similar findings. Sarcopenic patients had a significantly worse prognosis than those without, which was more prominent in patients with early-stage NSCLC[21]. Overall, there is mounting evidence that loss of muscle mass and strength, concomitant with an insidious functional decline, are strongly associated with unfavorable surgical outcomes.

Even though the principal findings of these studies have garnered traction among clinicians in using sarcopenia as an objective tool to identify high-risk patients and a predictor of outcomes, several recurring flaws were presented. These included the retrospective[11,15,16,18-21] nature of the studies conducted in single-center[12,17,20] settings in which sample sizes were limited[10,11,17,19-21], decreasing statistical power. The paucity of large prospective studies might be a potential source for selection bias, confounding factors and absent data. Furthermore, relationships between sarcopenia and other variables could not be analyzed due to inadequate cases. Next, as there is currently no universally accepted definition of sarcopenia, a wide spectrum of methodologies and cut-off values were utilized in these studies[10,12,14,15,21]. Just for muscle mass assessment alone, measurement techniques range from dual-energy X-ray absorptiometry, computed tomography, and bioelectrical impedance analysis, which may complicate the results. In addition, most studies depended solely on muscle mass evaluated by tomograph, as it is routinely examined by clinician, whilst neglecting functional criteria such as muscle strength[11,14,17], which is known to be a better predictive factor of adverse results. Another drawback was the variation in regions of muscle quantified such as the total skeletal muscle area in the third lumbar vertebra or the total psoas muscle area. Moreover, each study utilized slightly different threshold for defining low muscle mass or segregated their patient cohorts into tertiles to arbitrarily determine sarcopenic groups. Lastly, the findings were derived mostly from single-center studies that focused on a particular ethnic group, indicating that the results may not be representative of the general population[14,16,17]. All these variables could cause significant heterogeneities and

affect the validity of the results.

Nevertheless, the data provides a solid foundation to carry out multi-institutional prospective studies in the near future to circumvent the abovementioned limitations and reaffirm the results. Once these findings are validated and provides irrefutable evidence demonstrating a causal relationship between sarcopenia and adverse surgical outcomes, standardized method of assessment for sarcopenia and cut-off values can then be established. The results also reiterated the importance of conducting a preoperative evaluation for the diagnosis of sarcopenia as part of risk assessment during the planning for surgical procedures. Being able to stratify patients according to the severity of their condition as diagnosed according to the EWGSOP or AWGS consensus will allow the formulation of personalized intervention to diminish its impact on the patient's health. Nevertheless, sarcopenia is a remediable risk factor that can be mitigated prior to surgery and may have profound effects in postoperative recovery.

ENHANCED RECOVERY AFTER SURGERY – WHY DO WE NEED SOMETHING BETTER?

It has been two decades since the conceptualization of enhanced recovery after surgery (ERAS) protocol in 2001 by Fearon and Ljungqvist[22]. During these two decades, the principles of ERAS have been refined and assimilated into numerous types of surgeries[23-26]. The aim of the ERAS protocol has been to “develop perioperative care and to improve recovery through ... evidence-based practice”. However, the full adoption of the ERAS protocol has been difficult. In 2007, the ERAS Society recognized that simply having a protocol was insufficient to change widespread medical treatment, and more accurately, surgical practice[27]. Despite the efforts by various affiliated societies like the European Society for Clinical Nutrition and Metabolism and the International Association for Surgical Metabolism and Nutrition, the ERAS protocol is still yet to be fully adopted[28-30]. Recent evidence has shown that compliance to the protocol ranges only about 60%-65% at best, with a study from Singapore indicating that only 26.7% of surgeries adhered to > 70% compliance to ERAS principles[31]. When split into the pre-, intra- and post-operative components, one study revealed that postoperative protocol compliance was only 30%[30].

Despite having a consensus protocol supported by evidence, the lack of compliance by practitioners is most definitely multifactorial. Firstly, the ERAS principles require a mindset shift of not just a single specialty, but multiple. These include patients, nursing staff, surgeons, intensivists, anesthesiologists, and even the higher hospital administration. Everyone needs to be involved in the implementation of these protocols, and convincing such a diverse field of professionals to modify their practice is a tall order. Secondly, compliance has shown to be critical for patients to reap the benefits of the entire protocol[32,33]. Gianotti *et al*[32] highlighted in a multicenter prospective study that a > 70% compliance to ERAS had a 0.413 odds of having a lower overall surgical morbidity. There are more than 20 principles of ERAS distributed between pre-, intra- and post-operative components, rendering it logistically and technically challenging to fully comply. Thus, having a simpler system might actually allow greater compliance and thus, greater benefit to the patients. Having an overly complex system without accessory support (clinical coordinators, clinical champions, *etc.*) will inevitably result in poorer compliance. Thirdly, a majority of rehabilitative programs begin after surgery and in order for patients to reap the most benefits, a multitude of studies have advocated at least 1-2 mo of rehabilitation [34-36]. However, upon discharge, patients' compliance to the exercise and nutrition regime is often at best 70%[28-31]. Having the mentality that surgery is the definitive step in the removal of their pathology is a misconception that needs to be weeded out. A plausible reason for higher compliance to a prehabilitative program can stem from the fact that patients want to optimize their body in the lead up to their surgery, thus remaining cooperative to the nutritional and exercise interventions[37,38]. Most importantly, a lack of flexibility to tailor intra- and post-operative treatments will greatly impair the surgeons' compliance to the protocol[39].

Surgery is often mistaken as just a technical procedure; a completion of steps one to twenty for the “treatment” to be completed. In truth, just like any field in medicine, surgery is an art. Not every colectomy is the same to the one before. There are intricacies of the procedure, the aggressiveness of the tumor, the differences in technical challenge, and more crucially, the surgeons' concern for every case may differ. As such, requiring a surgeon to conform to the same intra- or post-operative

management of every surgery is inherently impossible since every procedure is distinct. By adhering to the ERAS protocol, surgeons may feel that their “control” over the patient’s progress is, in a way, removed from their hands. This can be difficult to accept especially when they have to shoulder the responsibility or any subsequent morbidity and mortality. It is in the authors’ opinion that implementing a personalized prehabilitation program will alleviate the surgeon’s emotional investment and enhance professional capacity during the procedure. As such, the compliance to such a program would likely surpass that of ERAS.

This concept has its detractors, of course, with one single-center randomized trial comparing a prehabilitation and rehabilitation program for frail patients undergoing minimally invasive colorectal resections[40]. Of the 110 randomized, there was no difference in 30-d surgical morbidity, length of hospitalization, readmission within 30 d from operation, and other patient reported outcomes measures. However, one may argue, looking at the numbers, that it might be insufficiently powered when their primary outcome measure was complication rates, with minimally invasive colectomies complication rate in tertiary institutions being < 10%.

WHAT IS PREHABILITATION? – ORIGIN AND COMPONENTS

The negative physiological effects of a major surgery include muscle proteolysis due to postoperative hypercatabolism[41], systemic inflammation[42], and pulmonary complications[43]. All these may culminate in muscle atrophy, loss of muscle strength, reduction in cardiorespiratory fitness and a decrease in oxidative capacity. For vulnerable surgical patients who are frail, elderly or sarcopenic, the inability to withstand the insult of a surgery is greatly amplified due to depleted physiological reserve, further diminishing the odds of recovery. The presurgical period represents a window of opportunity to boost and optimize the health of an individual, providing a compensatory “buffer” for the imminent reduction in physiological reserve post-surgery. Prehabilitation is the process of augmenting a patient’s functional capacity through various preoperative regimes to withstand a forthcoming stressor, with the goal of improving postoperative outcomes. As a multitude of factors such as the physical, psychological, and nutritional status of a patient significantly impact the success of a surgery, prehabilitation programs are trending towards a multimodal approach. These encompass physical exercises, nutritional optimization and psychological support. The synergistic effects of targeting key elements of a patient’s overall health condition can maximize surgical treatment outcomes.

NUTRITIONAL SUPPLEMENTATION

Nutritional status has been shown to be an independent predictor of postoperative complications in patients[44,45]. For example, preoperative serum albumin concentration, which is a surrogate marker for nutritional status, has been associated with morbidity, mortality, and LOS[46-48]. In one study, following anterior cervical discectomy and fusion, hypoalbuminemic patients had a significantly longer hospital stay relative to patients with normal serum albumin of 5.00 d and 1.88 d, respectively [44]. Hence, nutritional conditioning aims to identify and rectify areas of deficit to increase functional reserve preoperatively, minimizing the risk of adverse outcomes. It is important to recognize that nutrition supplementation does not adhere to the “one-size-fit-all” approach. For example, a systematic review highlighted that carbohydrate loading (CL) during the preoperative phase significantly reduced insulin resistance in patients[49]. On the contrary, preoperative CL increased postoperative tumor proliferation and exacerbated clinical outcomes in estrogen receptor positive T2 patients [50]. Depending on the disease, surgical procedures and nutrition deficits, concomitant with an appropriate nutrition screening, a targeted program can be formulated to optimize an individual’s reserve. Nevertheless, the overall goal is to increase nutrient stores and metabolic reserve while augmenting physical strength to improve postoperative recovery.

There is no standardized regime specifically for patients with sarcopenia, with the type of nutrition, amount and duration varying between studies. A majority of prehabilitation programs focus mainly on protein supplementation for the purpose of anabolism. The pathogenesis of sarcopenia is multifactorial and implementing a nutritional intervention has to address a plethora of signaling pathways. Firstly, there is a dysregulation of anabolic and catabolic networks[51], favoring disproportionate

muscle protein breakdown rather than synthesis. In some studies, branched-chain amino acids, which constitute three of the nine essential amino proteins, were supplemented preoperatively. These amino acids, in particular leucine, play a vital role in the regulation of anabolic signal transduction[52]. Leucine activates the mammalian target of rapamycin (mTOR) signaling and eukaryotic initiation factor 4G that promote translation and protein synthesis[53]. In addition, branched chain amino acids has been demonstrated to attenuate protein degradation rate[54,55]. Another common form of protein supplementation is the provision of whey protein, which is extracted from the whey that remains after milk is curdled and strained, containing all nine essential amino acids. Whey protein consists of a high proportion of branched chain amino acid, augmenting anabolic processes[52]. In addition, whey has high amount of cysteine, the rate-limiting amino acid for the synthesis of intracellular glutathione, the dietary antioxidant. This additional redox defense may be beneficial as oxidative stress has been shown to increase in sarcopenia[56] and induce during surgical stress response[57,58]. Next, sarcopenic patients manifest a heightened inflammatory state [59], associated with high levels of proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α) and macrophage migration inhibitory factor[60-62]. The added benefit of whey protein is that it contains α -lactalbumin and lactoferrin, which have been demonstrated to inhibit the production of proinflammatory cytokines such as TNF- α and IL-6 in rat and human myogenic cells[63,64].

As muscle is the principal site of glucose disposal and plays a paramount role in maintaining blood glucose homeostasis, it is deemed to be the primary determinant of whole-body insulin resistance. Numerous studies have shown that sarcopenia and skeletal muscle mass are associated with impaired fasting glucose, diabetes, and insulin resistance[65-68]. The condition is exacerbated during surgery in which insulin resistance is a central metabolic change during surgical stress. Insulin resistance is known to be associated with an increased risk of complications, morbidity and an independent factor influencing LOS postoperatively[69,70]. One noteworthy strategy employed in several studies is perioperative CL to mitigate the impact of surgical stress. CL has been demonstrated to significantly diminish insulin resistance and, in some cases, halved the initial value[49,71]. In brief, CL suppresses the expression of muscle pyruvate dehydrogenase 4, alleviating the inhibition of the pyruvate dehydrogenase complex, allowing pyruvate to enter the Krebs' cycle. In addition, CL augments PI3K activity and expression of protein kinase B, which are important mediators of the insulin signaling pathway, ameliorating peripheral insulin resistance[72]. Secondly, CL has shown to attenuate depletion of muscle mass after elective abdominal surgery [73]. However, the available data pertaining to CL and postoperative outcomes in sarcopenic patients is limited, and more studies are required to investigate this association and optimize this aspect of enteral nutritional support.

Other nutrients may play a vital role in complementing or augmenting the protein anabolic response. For example, vitamin D is a steroid hormone that modulates muscle anabolic state and muscle energy metabolism[74]. In addition, it plays an important role in regulating the body's levels of calcium and phosphorus, which are responsible for controlling muscle contraction, relaxation, and function[75]. Vitamin D is commonly reduced in elderly subjects[76,77] and its deficiency is associated with disruption of mitochondrial function, oxidative stress and muscle atrophy[74,78]. Hence, it is not surprising that in elderly subjects, supplementing vitamin D was shown to enhance muscle mass and chair-stand test time, a surrogate of muscle power [79]. This can be partly attributed to the improvement of mitochondrial oxidative function in skeletal muscle. Furthermore, a meta-analysis of 13 randomized controlled trials (RCTs) in elderly subjects above 60 years highlighted that vitamin D supplementation elicited beneficial effects on strength and balance[80]. Next, omega-3 fatty acids, which has shown to augment the protein anabolic response and exert anti-inflammatory properties[81], can potentially be a useful dietary supplement to improve muscle health. In one study, omega-3 fatty acid augmented muscle protein synthesis (MPS) in healthy older adult, most likely by an increased activation of mTOR [82]. Additionally, sarcopenic patients have been shown to manifest reduced level of circulating vitamin B12, which have a prominent role in modulating muscle strength and function[83]. Supplementing vitamin B12 may have a direct impact on muscle performance and physical function in high-risk patients. Other supplements, such as epicatechin[84] and urolithin A[85], found in pomegranate, are also interesting options that have proven to improve muscle growth factors and modulate skeletal muscle mitochondrial gene expression, respectively.

PHYSICAL ACTIVITY MODIFICATION

The main objective of exercise prehabilitation is to improve physiological reserve and fitness, which are modifiable risk factors that can reduce surgical complications. Two fundamental components of exercise prehabilitation are aerobic/endurance and resistance/strength exercises. In the context of high-risk population such as frail or sarcopenic patients, they may benefit more from such exercise prehabilitation. Firstly, the concept of aerobic training is to improve an individual cardiovascular fitness through a prolonged period of low contractility that depends mainly on slow-twitch muscle fibers. This extended, yet low intensity, form of physical activity has been shown to induce mitochondrial biogenesis, ATP production, muscle mass, and strength in older subjects[86-89]. Mechanistically, aerobic exercise activates the energy sensing network that involves AMPK, p38 MAPK, and SIRT1 proteins[90-92]. These proteins initiate the mitochondrial biogenesis program through the activation of the transcriptional co-activator PGC-1 α . This in turn drives mitochondrial gene transcription through a subset of transcription factors. Next, aerobic exercise has been demonstrated to reduce the expression of catabolic genes[93,94] and increase MPS[95] in older subjects. Furthermore, exercise may increase the expression of autophagy-related proteins in skeletal muscle[96], a process vital in basal myofiber homeostasis and muscle integrity.

Alternatively, resistance exercise aims to induce muscle hypertrophy and strength *via* a short period of high contractility against an external load. It is dependent on fast-twitch muscle fibers that are able to generate a bigger force but fatigue quickly. Resistance training (RT) is critical in preventing muscle atrophy because it stimulates protein synthesis and hypertrophy, enhancing muscle strength. In the context of sarcopenic patients, the favorable effects of RT include increase in muscle mass, strength, quality and functional performance[97-99]. Mechanistically, RT activates the mTOR pathway, a central mediator of protein synthesis and skeletal muscle size[100]. Concomitantly, RT upregulates extracellular signal-regulated kinase 1/2, modulating translation initiation and protein synthesis[101]. Both these mechanisms underlie the resistance exercise-induced anabolic responses. In addition, after RT exercises, testosterone levels have been shown to increase in the sarcopenic group[97], the main physiological anabolic hormone that maintains muscle mass and function. RT has a dual effect in which it suppresses catabolic networks that drive muscle degradation and atrophy. For example, it is known to reduce myostatin concentration[97], a member of the transforming growth factor β family. Myostatin is a potent negative regulator of skeletal muscle regeneration and growth. The myokine also inhibits myogenic cell proliferation, myoblast fusion and the expression of several muscle-specific genes[102]. Furthermore, RT has been demonstrated to attenuate the expression of FOXO3a and MuRF1[89,94], which are part of the ubiquitination cascade that results in the degradation of myofibrillar proteins.

In summary, both forms of physical exercise elicit different beneficial outcomes. Aerobic training has a greater influence on mitochondrial dynamics and cardiovascular fitness, while RT is more effective in increasing muscle mass and strength. As both muscle strength and cardiorespiratory fitness decline during the postoperative period, it is conceivable that the combination of these exercises can offer the advantages of both. Numerous studies have adopted a well-rounded exercise program to reap the synergistic effect in improving functional reserve and fitness in older adults[103,104]. Beyond the physical enhancement, exercise is recognized to decrease pro-inflammatory cytokines and boost plasma levels of anti-inflammatory ones, creating an anti-inflammatory environment[105]. In addition, the anti-oxidative effects of exercise *via* decreased ROS production, a greater mitochondrial capacity to scavenge free radicals, and enhanced antioxidant defenses[106], further reiterate the need to incorporate exercise programs in combating sarcopenia.

Ideally, the exercise intervention ought to be targeted and individualized to optimize surgical outcomes. Factors, such as baseline functional capacity, nutritional status, frailty status and patient's compliance have to be taken into consideration. Due to disease heterogeneity and diverse patient profiles, it is not surprising that an optimal prehabilitation exercise regime has not been defined, often differing in duration, intensity and frequency. Nevertheless, the various repertoire of exercise programs implemented have a collective goal at improving functional capacity. In general, a baseline assessment of functional capacity is first performed to provide an initial benchmark for reference. Two frequently used tests are the cardiopulmonary exercise test and the 6-min walk test. From the initial assessment, a multidisciplinary group can formulate an intervention that best suits the patient that optimizes surgical outcomes. Throughout the prehabilitation period, the patient must be reviewed

regularly in order to verify if the stimulus is adequate or excessive. Parameters, such as body composition measurement, muscle strength, heart rate, and fatigue level, have to be meticulously recorded.

PSYCHOLOGICAL PREPARATION AND MOTIVATION – THE BELITTLED YET CRUCIAL COG

It is evident that psychological distress is associated with negative surgical outcomes [107]. Anxiety and depression can lead to higher levels of pain [108] and non-compliance with prehabilitation programs, severely compromising its impact. In brief, negative emotions may heighten pain sensitivity and preoperative stress may induce glucocorticoid productions that delay wound healing [108,109]. This is especially detrimental for high-risk patients who have low functional reserve and may worsen health status or delay postsurgical recovery. In one retrospective cohort study, elderly patients that underwent surgery for lumbar spinal stenosis demonstrated that anxiety was identified as a preoperative factor that influenced patient satisfaction with surgery [110]. The authors highlighted the importance of evaluating the preoperative psychological state of elderly patients undergoing such surgery. There are studies that have also shown that cognition and psychological well-being were significantly associated with mortality in elderly patients undergoing surgery [111,112]. In addition, several psychosocial factors, such as anxiety, increased the likelihood of adverse outcomes in frail elderly patients, which included long LOS and rehospitalization [113]. Interestingly, psychosocial factors have indicated to be associated with reduced muscle mass, strength, and function in elderly subjects [114].

Patients can first be screened for anxiety and depression using the GAD-7 and PHQ-9 questionnaires. Psychological interventions can then be put in place for those detected at high-risk to alleviate the stress of surgery or for psychological support. These include referral to a psychologist, cognitive behavioral therapy, and relaxation and breathing techniques [115-117]. To realize the future of modern healthcare and increase efficiency of health systems, integration of technology in clinical treatment is paramount. This will allow facilitation of psychological interventions to markedly improve the health status and well-being in older patients. Technology-based interventions, such as virtual reality, robots, and smartphone applications, have the potential to support psychological treatment in high-risk patients [118]. Overall, despite the body of evidence demonstrating that cognitive and psychological status are vital components of health in high-risk patients, it is often neglected and not used in determining the risk of adverse postsurgical outcomes. The identification of these factors can assist in patient care planning and to detect patients who may not be able to withstand the stress of surgery.

ALL HANDS ON DECK – A MULTIMODAL APPROACH TO PREHABILITATION

In older or sarcopenic patients, anabolic resistance in muscle is observed, in which the muscle exhibits a blunted response to anabolic stimuli, such as intake of protein and resistance exercise [119,120]. Factors such as insulin resistance, chronic low-grade inflammation and physical inactivity have been shown to be contributors to this phenomenon [121,122]. Mechanistically, several signaling networks are involved in modulating the diminished rate of MPS despite the presence of an anabolic stimulus. In brief, a dysregulated AKT-mTOR signaling is likely to be implicated for the reduced response to anabolic stimuli [123]. An increased basal expression of inflammatory cytokines, like NFκB, TNF-α and IL-6, are known to suppress muscle anabolism by impairing protein synthesis *via* the mTOR pathway [124-126]. Therefore, it may be efficacious to induce both anabolic stimuli, ensuring that it is adequate for the coordinated increase in MPS. The synergistic effects of exercise and nutrients, in particular amino acids, provide the requisite anabolic environment and building blocks to support protein synthesis. It is well documented that nutrient intake during post-exercise period is needed to bring about a positive net protein balance. This is associated with increased phosphorylation of components of the mTOR signaling cascade beyond levels that are detected following exercise without nutrients [127,128].

In the elderly, several studies have attested to the additive effects of exercise and nutrition, with a greater rate of protein synthesis than feeding alone[129,130]. In addition, another systematic review demonstrated that a combination of exercise and amino acid-based nutrition was sufficient to induce a comparable MPS response between young and older individuals compared to either intervention alone[131]. As highlighted by the authors, the exercise volume and nutrient quantity must be above a certain threshold to stimulate equivalent MPS rates in young and older adults, below which age-related muscle anabolic resistance may become apparent. In the same vein, the functional benefits of implementing both interventions are observed in patients with sarcopenia as well. For example, RT and epicatechin supplementation demonstrated the greatest improvement on improving muscle growth factors and preventing the progression of sarcopenia in sarcopenic older patients[84]. Similarly, a meta-analysis carried out involving 429 sarcopenic elderly highlighted that nutritional supplement boosted the effects of exercise intervention such as an increase in muscle mass, strength and physical performance[132]. Another meta-analysis that included data from 22 RCTs and 680 subjects corroborated the previous findings in which protein supplementation augmented the adaptive response of the skeletal muscle to prolonged resistance-type exercise training in both younger and older population [133]. The additional gains in muscle mass and strength are especially important for older or sarcopenic patients to increase their functional capacity to withstand the stress of a surgery. In one study, elderly patients scheduled for colorectal cancer surgery underwent a prehabilitation program that involved physical and nutrition interventions with relaxation exercises to reduce anxiety[134]. Patients in the prehabilitation group significantly increased the amount of physical activities that they performed, which translated into improvements in functional walking capacity. Over the years, there is a radical change in prehabilitation programs, pivoting from unimodal to multimodal approach, due to the synergistic effects observed in a plethora of studies. It is incumbent on us to build upon these results and to evaluate its beneficial effect on surgical outcomes in high-risk patients.

PREHABILITATION FOR THOSE WHO WOULD TRULY BENEFIT - HIGH-RISK PATIENTS

The focus of this review is to evaluate the impact of prehabilitation programs on a subset of high-risk patients that are elderly, frail, or manifest characteristics of sarcopenia. This allows healthcare professionals to recalibrate their approach in managing this vulnerable population, optimizing a prehabilitation program that is tailor-made to individual patient based on the totality of data presented.

ELDERLY PATIENTS

It is evident that implementing prehabilitation programs have immense benefits in improving postsurgical outcomes for elderly patients. In one study, elderly patients undergoing elective abdominal cancer surgery took a preoperative comprehensive geriatric assessment for interprofessional preoperative evaluation and care coordination[135]. The preoperative assessment team focused on a holistic perioperative health optimization that encompassed cognitive, functional, and nutritional status. Patients in the intervention group manifested more desirable health outcomes in the postoperative period, with a reduction in the median LOS, lower readmission rates, fewer mean number of complications, and improvement in independence on discharge. However, there was a significantly higher incidence of delirium, a common complication in elderly patients undergoing major abdominal surgery in the intervention group. The authors postulated that the screening conducted by the program most probably attributed to the increased detection that was previously underdiagnosed in the control group. On the contrary, patients aged 70 years and older undergoing elective abdominal surgery for colorectal carcinoma or aortic aneurysm had significantly reduced incidence of delirium upon completion of the prehabilitation program[136]. Hence, embarking on a prehabilitation program can potentially be helpful in mitigating the risk of developing post-surgery delirium, warranting further investigations with higher quality study designs. To further reiterate its beneficial effects, another prehabilitation regime that comprised of endurance exercise training and nutritional intervention reduced the number of

elderly patients with postoperative complications undergoing major abdominal surgery compared to control group[137]. In a similar vein, another study investigated the impact of a comprehensive multidisciplinary care program that consisted of both prehabilitation and rehabilitation components[138]. It was implemented for elderly patients that underwent elective surgery for stage I-III colorectal cancer that included exercise, nutrition and psychological interventions. Patients who followed the whole multimodality program or partook a portion of it exhibited a significant reduction in prolonged LOS and severe complications. However, the merger of both prehabilitation and rehabilitation components meant that the role of prehabilitation alone could not be assessed, and more studies are required to independently evaluate its effectiveness. However, several findings did demonstrate that even though prehabilitation did not negatively impact postoperative course in elderly subjects, it did not elicit any significant beneficial effect[139-141].

These results merit further investigation to evaluate the effectiveness of preoperative regimes in elderly patients. Higher quality clinical research studies must be conducted to address shortcomings such as small sample size, flawed research designs and a limited range of surgical specialty. There are several key factors that may be imperative in developing successful prehabilitation programs for geriatric patients. Firstly, a comprehensive geriatric assessment is vital to evaluate the health status of patients and to formulate the appropriate treatment plans. A qualified team of clinical professionals has to be designated to conduct, develop, implement and monitor the entire process. Next, stratifying patients who are at higher risk of developing adverse postoperative outcomes allows personalization of the interventions. The program can then be modified, such as modulating the frequency and intensity of an exercise, or devising a nutrition plan that optimizes the patients' physiological reserve. It is also advisable to track the metabolic and functional changes of the patients at specific timepoints to monitor the effectiveness of the prehabilitation program.

FRAIL AND SARCOPENIC PATIENTS

Frailty and sarcopenia are common age-related conditions that are associated with adverse surgical outcomes. Therefore, these group of patients may gain more from undergoing prehabilitation programs that can substantially improve their physiological capacity. In one study, frail patients undergoing elective oncologic surgery of upper gastrointestinal tract were stratified based on their frailty status[142]. Those patients that underwent a multidisciplinary preoperative management plan that included oral nutritional support and aerobic exercises had a significant reduction in 30-d and 3-mo mortality rates, together with a decrease in overall and severe complication rates compared to control group. These likely translated to a shorter LOS observed but did not reach statistical significance. Due to the physical or socioeconomic status of a patient, it may not be feasible to conduct a prehabilitation program in the host institute. Hence, a home-based approach is a viable option, even though it may not be optimal for the patients to do or for investigators to collect data. For example, frail patients undergoing major colorectal resection partook a multimodal prehabilitation program either at home or in the day rehabilitation center [143]. The mean length of hospital stay was significantly shorter for patients that underwent the program compared to the control group, indicating the possibility of implementing a trans-institutional approach in the home setting. Nevertheless, only a minority of patients in the intervention group were frail (26.4%), and a subgroup analysis should be carried out to validate the findings. Another systematic review carried out supported the growing body of evidence, reiterating the importance of prehabilitation programs to gear towards a multimodal approach to maximize its effectiveness in improving health status prior to surgery[144]. This review interrogated the role of prehabilitation and surgical outcomes in frail surgical patients. In summary, the studies that implemented a multimodal program, which included preoperative exercises and nutrition interventions, led to a reduction in mortality and duration of hospital stay[143,144]. On the other hand, studies that implemented an exercise intervention alone did not demonstrate any significant difference in postoperative functional recovery[145-147]. Nevertheless, limitations of these studies included the use of various frailty indices, risk of bias and small sample sizes. These have to be addressed in large randomized controlled studies to determine the validity of the results.

On the contrary, there are findings that call in question the effectiveness of prehabilitation programs in eliciting favorable outcomes in high-risk patients. One study indicated no statistical significance in postoperative outcomes when implementing the same multimodal program preoperatively or postoperatively in frail patients undergoing predominantly minimally invasive colorectal cancer resection[40]. The authors listed reasons that could have accounted for the lack of effect of prehabilitation observed in the trial. Firstly, the simultaneous implementation of an established enhance recovery pathway might have masked the impact of an unoptimized prehabilitation program. In addition, the authors also hypothesized that the duration of the program, which lasted a maximum of 5 wk, might be inadequate to raise functional reserve to a threshold level that substantially mitigated negative surgical outcomes. The use of a rehabilitation control group rather than the usual care or a sham intervention made the study more clinically relevant. However, this might have limited the effects observed in patients that underwent the prehabilitation program. Nevertheless, the sample mainly consisted of a niche group of frail patients undergoing minimally invasive surgery under very specific context of care. Hence, the results may not be generalizable, and more trials have to be conducted to have a conclusive finding. Next, a multi-center, single-blinded RCT involving frail older patients from two university hospitals undergoing elective colorectal cancer surgery demonstrated minimal effects despite implementing tailored prehabilitation interventions[148]. Compared to control group, the rate of Grade II-V complications, readmission or mortality were not significantly reduced in the intervention group, only experiencing fewer less severe complications. Even though this study did carry out preoperative geriatric assessment, the authors acknowledged that the absence of a multi-professional team could have led to the formulation of interventions that were suboptimal in improving preoperative physical functions. In addition, the median intervention time was reduced from the initial stipulated duration of 21 d to only 6 d, which could have drastically affected the outcome. Hence, the validity of the results must be carefully scrutinized, and these limitations have to be circumvented to evaluate the profound effects of prehabilitation on these group of patients.

The studies interrogating the impact of prehabilitation on surgical outcomes in sarcopenic patients are limited. In a pilot study, the authors evaluated a preoperative exercise and nutritional support program for gastric cancer patients with sarcopenia undergoing gastrectomy[149]. After the completion of the program, the sarcopenic patients exhibited an enhancement in functional capacity, with a significant increase in handgrip strength and a non-significant improvement in gait speed with increased muscle mass index. Four patients became non-sarcopenic before surgery after an increase in their body weight and handgrip strength were observed, indicating the beneficial effect of the program. However, postoperative complications were not significantly different between both the enrolled sarcopenic and non-sarcopenic control patients. Nevertheless, the authors acknowledged that a well-designed RCT is needed to circumvent the small sample size, lack of a control group and the program framework for the results to be conclusive. In another study that can further rationalize the need for a prehabilitation regime demonstrated that perioperative oral nutritional supplementation decreased prevalence of sarcopenia following radical cystectomy compared to multivitamin control group[150]. The number of sarcopenic patients did not increase during the preoperative period for those that received oral supplementation whereas there was a significant increase of 20% for the control group. Postoperatively, there was a trend towards a lower incidence of complications and readmissions, but the result was not statistically significant. Overall, further evidence from larger RCTs is mandatory to not only investigate the effects of personalized prehabilitation program and surgical outcomes in high-risk patients, but also to optimize the process in carrying out preoperative geriatric assessment and the parameters of the program.

RESOURCE ALLOCATION TO OPTIMISE HEALTHCARE VALUE-DRIVEN OUTCOMES

The above has demonstrated overwhelming evidence of the utility and benefit of prehabilitation. However, should it be applied for everyone - a one-size-fit-all? Statistics from America demonstrates a worrying trend of exponential healthcare spending, which is showing no signs of relenting. In order to yield maximum benefit from the money spent coordinating and executing prehabilitation programs, the authors opine that it may actually benefit patient groups with the most risks of

morbidity and mortality, such as those with sarcopenia or frailty. Frailty is a state of functional decline due to the loss of muscle mass[151]. Age-related sarcopenia is a multi-organ process that lead to a loss of skeletal muscle mass with a resultant decline in physical functions[152,153]. A recent news article suggested that the onset of sarcopenia may be as early as from the fifth decade of life. Along with the patients' comorbidity burden, these would negatively affect surgical outcomes, resulting in increased complication rates and a higher propensity of delay to return to baseline [154-157]. These would naturally result in higher healthcare costs.

Even though nutrition and resistant training have shown positive effects on sarcopenia, the process and regulatory mechanisms of sarcopenia is poorly understood [158,159]. Needless to say, how these interventions affect the mechanism of sarcopenia is much less well understood. Thus, a multi-modal, multi-disciplinary tailored prehabilitation program, equipped with military-like precision and coordination, will be well-poised to optimize these higher risks patients before their surgeries. This is only feasible with adequate funding by hospital administration or governmental level healthcare funding.

There has yet to be convincing evidence that prehabilitation in a high-risk patient group would definitely translate to cost efficiency. A recent systemic review of prehabilitation in frail surgical patients was not able to conclude cost effectiveness as there were only 5 studies isolated[160]. However, the study recommended that frailty assessment should still be included in the recruitment into prehabilitation and that such a program would lessen operative risk. One can extrapolate that by focusing on high-risk patient groups, those that would be anticipated to require more healthcare resources than those who are healthy, there will be a higher chance of improving their baseline physiology in the short time before to their procedure[161,162]. This, in turn, would potentially have the largest clinical difference post-operatively amongst all other patient groups. Therefore, in terms of resource allocation, it would make most sense to focus on those who are of highest risk of surgical morbidity.

HOW TO MAKE EXISTING PREHABILITATION EVEN BETTER?

The identification of patients who will benefit from prehabilitation requires improvement from all fronts. Clinicians, especially the surgeons, will require a mindset change from a rehabilitation-centric focus to that of prehabilitation. Surgeons will not only need to embrace the fact that surgery might be delayed due to prehabilitation, but more importantly, be active in looking out for patients who will actually benefit from it. The underlying objective is to optimize their baseline function prior to surgery with the intention of reducing postoperative risks, improving surgical, oncological and patient-reported outcomes like quality-of-life. In order to assist clinicians to identify such patients, a consensus set of biomarkers derived from sound scientific and clinical evidence is required. At the moment, such a list of biomarkers is varied and non-specific, being only able to correlate with sarcopenia or frailty, but unable to concurrently correlate with postoperative outcomes[163-165]. Large scale investigations are required to unravel novel findings that can associate quantifiable biomarkers from patients such as muscle and functional health with surgical outcomes [166]. It is anticipated that a panel of functional and biochemical markers coupled with a receiver operating characteristic curve may eventually provide the most ideal predictive model. Having a simple yet accurate way of identifying patients who will benefit most from prehabilitation allows resources to be properly allocated. With this pragmatic approach in driving up the value of the program, it will have a better opportunity to be supported by various government-level or hospital-level administration.

More studies are required to integrate the different pillars of a multimodal prehabilitation program: Nutritional, physical and psychological interventions. This effort towards gaining a more in-depth understanding must go beyond that of just clinical studies. For example, how these interventions modulate molecular and genetic levels in muscle cells may be key to bringing us closer to revealing the optimal type of nutrition and exercise for prehabilitation. Equipped with this new knowledge, the surgical team would be better prepared to personalize and individualize prehabilitation to suit the needs of high-risk patients in this program.

Healthcare has advanced dramatically in the last 2 decades. Technology has become a well-incorporated cog of scientific and clinical practice. Pertinent to this discussion, deep machine learning, or artificial intelligence (AI), has been well recognized to have outperformed clinicians in some aspects of clinical practice[167-172]. AI may well have

a role to play in the identification, customization and monitoring patients in prehabilitation. What is crucial in deep machine learning is the vastness of clinical data which is best obtained from a varied patient population, through international, multi-center collaboration. Other vital technology that we need to learn to adopt for such a program may be applications, or “apps”, on personal smartphones or wearable devices. In 2020, more than 96% of the United States population owned a smartphone, including 95% of those in the lowest socioeconomic class[173]. In 2019, statistics from the United States shows that 56% of the population has at least one wearable device, with a further 13% keen to invest in such a device in 2020[174]. Apps on such devices not only act as a personal assistant to the patient or family to coordinate consultation hospital visits, but also to support the clinical team in monitoring patient’s compliance to diet and exercise regimes. The seamless coordination between the patients and healthcare professionals is an important aspect to achieve compliance, which would determine the success of such a program. Inevitably, patient embarking on such a rigorous program will have numerous appointments with reviewing clinicians, dietetics, physiotherapies and pre-anesthetic assessments. Prompts from such apps can help motivate patients and provide feedback to the clinical team, enabling appropriate mediation when necessary. Such early attempts to improve the patients’ compliance during this trying time will improve health outcome leading up to major procedure

CONCLUSION

The world population is aging at an unprecedented rate concomitant with a remarkable increase in life expectancy. It is not surprising that the geriatric surgical population is also rapidly growing, and hence, clinicians have to take into account additional risk factors, such as frailty. In particular, it is evident that sarcopenia is an independent predictive factor of postoperative outcomes that has to be mitigated prior to surgery. Prehabilitation represents a paradigm shift in geriatric surgical care, with the goal of enhancing functional capacity to withstand a forthcoming stressor. Emerging data has inspired healthcare professionals to not only adopt a multimodal approach, but also to pivot towards personalized programs. We have reviewed the synergistic effect of the various pillars in improving surgical outcomes in high-risk patients. Nevertheless, it is mandatory to further optimized these programs by carrying out well-designed, multicenter, prospective study. In addition, it is vital that clinicians continue to work closely with scientists to unravel the signaling networks driving the progression of sarcopenia and mechanistic underpinnings of each intervention. These strategies will allow novel prehabilitation programs to be formulated that can be customized for each patient.

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