

## Prehabilitation: High quality evidence is still required

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## Summary

Prehabilitation comprises multidisciplinary healthcare interventions, including exercise, nutritional optimisation and psychological preparation, which aim to dampen the metabolic response to surgery, shorten the period of recovery, reduce complications, and improve the quality of recovery and quality of life. This editorial evaluates the potential benefits and limitations of and barriers to prehabilitation in surgical patients. The results of several randomised clinical trials and meta-analyses on prehabilitation show differing results, and the strength of the evidence is relatively weak. Heterogeneity in patient populations, interventions and outcome measures, with a wide range for compliance, contribute to this variation. Evidence could be strengthened by the conduct of large scale, appropriately powered multicentre trials that have unequivocal clinically relevant and patient-centric end points. Studies of prehabilitation should concentrate on recruiting patients who are frail and at high-risk. Interventions should be multimodal and exercise regimens should be tailored to each patient's ability with longitudinal measurements of impact.

The earliest references to “prehabilitation” originate in the military literature where prehabilitation centres were set up to transform substandard recruits into standard ones, with men of poor physique being sent to these centres for physical development and correction of remedial defects.<sup>1, 2</sup> Preoperative and postoperative exercise for patients undergoing gynaecological surgery was proposed as early as 1959,<sup>3</sup> but the concept of preoperative rehabilitation or prehabilitation only gained popularity in the 21<sup>st</sup> century.<sup>4</sup> Prehabilitation comprises multidisciplinary interventions, including exercise, nutritional optimisation and psychological preparation, designed to dampen the metabolic response to surgery, shorten the period of recovery, reduce complications, and improve the quality of recovery and quality of life. We aimed to evaluate the potential benefits and understand the limitations of and barriers to prehabilitation.

### **The rationale for prehabilitation**

The catabolic response to major surgery is well known and the systemic proinflammatory response is accompanied by muscle inflammation and metabolic dysregulation both at and remote to the site of surgery at the level of gene and protein expression, with interleukin-6 as a main driver.<sup>5</sup> Moreover, muscle mitochondrial function is acutely impaired after surgical trauma, as evidenced by suppressed muscle pyruvate dehydrogenase complex activation and maximal mitochondrial ATP production.<sup>6</sup> The proposed advantages of prehabilitation are that exercise training, psychological support and nutritional interventions will place the patient in a better state to withstand the metabolic dysregulation and fatigue produced by major surgery. Prehabilitation might also help the

patient withstand postoperative complications better and facilitate earlier return to independent function<sup>4, 7</sup> (**Figure 1**).

### **Exercise interventions**

Although appreciable muscle growth cannot be expected with relatively short-term exercise interventions, improved aerobic capacity and metabolic flexibility (the ability to respond or adapt to conditional changes in metabolic demand) are possible,<sup>8</sup> such that patients might have a reduced risk of surgical complications and shorter hospitalisation.<sup>4, 9-12</sup> In practice, the precise exercise regimen varies greatly between studies, both in type of exercise and duration (2 to 12 weeks) between studies, and little is known about the dose-response relationship. It usually comprises supervised and unsupervised sessions with a combination of aerobic exercises and resistance training in varying proportions.<sup>9-13</sup> Professionally supervised sessions usually occur in hospitals with frequency ranging from one<sup>13-15</sup> to three 60-min session per week,<sup>10</sup> and they generally consist of more difficult, high-intensity exercises performed on sports machines (stepper,<sup>14, 15</sup> treadmill<sup>14</sup> or cycle ergometer<sup>10</sup>). Home exercises are based on 30 min of moderate intensity walking, either daily<sup>13, 15</sup> or three to four times per week.<sup>16, 17</sup> Alternative activities include jogging,<sup>13, 14, 16</sup> cycling<sup>14</sup> or swimming.<sup>16</sup> Some regimens are enforced strictly while others are based on patient abilities and preferences.<sup>13, 14</sup> Some programmes also focus on inspiratory muscle training consisting of deep breathing at full vital capacity, diaphragmatic breathing, and training in huffing and coughing techniques.<sup>13</sup> Static and dynamic stretching is frequently added as a top-up at the beginning and end of exercise to develop and maintain range of motion.<sup>11</sup>

High intensity interval training (HIIT) has been employed to improve patient adherence and compliance to prehabilitation training because of its relatively short nature (e.g., 5 × 1 min intense bouts of exercise three to four times per week). Such HIIT interventions have been reported to improve aerobic fitness (peak oxygen consumption) in patients with urological<sup>18</sup> but not colorectal cancer.<sup>19</sup>

The improvement in performance required to demonstrate improvement in surgical outcome in a specific patient remains to be elucidated and the impact on long-term outcomes is unknown.

### **Nutritional interventions**

Patients in whom surgery is planned should undergo nutritional risk screening and if found to be at risk, be referred to a dietitian for nutritional assessment.<sup>20</sup> Patients who are at nutritional risk or those who are malnourished should be given dietary advice or oral nutritional supplements.<sup>20</sup> With targeted nutritional therapy alone a meta-analysis of studies in older patients having surgery for abdominal tumours showed a reduction in postoperative complications.<sup>21</sup> There is little evidence to suggest that providing preoperative nutritional support for more than 14 days is of added benefit.<sup>20</sup> Continuation of oral nutritional support in the postoperative and after discharge might be of benefit, but the evidence is weak and conflicting.<sup>22</sup> A recent meta-analysis<sup>23</sup> and an umbrella review of meta-analyses<sup>24</sup> have shown that perioperative provision of immune modulating nutrition (containing arginine, nucleotides and  $\omega$ -3 fatty acids) reduced postoperative infectious complications and hospital length of stay when compared with controls. It is recommended

that if immune modulation is considered, it should be commenced 5-7 days preoperatively and continued postoperatively.<sup>20, 23, 24</sup> Another meta-analysis has shown that in patients undergoing colorectal surgery nutritional prehabilitation alone or combined with an exercise programme decreased hospital length of stay by 2 days.<sup>11</sup>

### **Psychological interventions**

The prospect of undergoing major surgery, sometimes coupled with a serious diagnosis like cancer, can be stressful and patients can experience fear, anxiety, isolation and frustration while awaiting surgery.<sup>25</sup> A qualitative study suggested that patients appreciate the offer of support from healthcare professionals to help them prepare for surgery both mentally and physically.<sup>25</sup> Patients also felt that management of surgical expectations and preparing them and their families or carers to recover at home helped them to be in a better mindset for recovery.<sup>25</sup> Interaction with and support from patients undergoing similar treatments were also motivational.<sup>25</sup>

Psychological interventions that may aid prehabilitation include cognitive-behavioural therapies, relaxation techniques, mindfulness-based interventions, coping strategies, hypnosis and narrative medicine.<sup>26</sup> Face-to-face or virtual coaching by accredited coaches can include discussion of health status, strengths recognition, resilience profiling and development, social and support systems, emotional management, and goal setting.<sup>9, 14, 16,</sup>

<sup>17</sup> A small study that utilised exercise therapy alone showed that prehabilitation had no effect on reduction of preoperative anxiety and depression.<sup>27</sup> A larger study that assessed the impact of a 4-week trimodal prehabilitation programme showed that although patients

in the prehabilitation group had reduced anxiety scores compared with controls, there was no reduction in postoperative morbidity, mortality or hospital length of stay.<sup>13</sup> A systematic review has suggested that perioperative psychological interventions are technically feasible and may reduce anxiety and pain.<sup>26</sup>

### **Prehabilitation *versus* rehabilitation**

Two randomised clinical trials have compared prehabilitation with postoperative rehabilitation in patients undergoing colorectal surgery.<sup>15, 16</sup> The first found that functional walking capacity increased significantly in 53% of the prehabilitation group (for 4 weeks before surgery) compared with 15% of the rehabilitation group (for 8 weeks after surgery). However, complication rates and length of stay were no different.

The second study randomised 110 frail patients to receive 4 weeks of prehabilitation or 4 weeks of rehabilitation after surgery.<sup>15</sup> There was no significant difference in the 30-day Comprehensive Complications Index. Overall and severe complications at 30-days, length of stay, readmissions, recovery of walking capacity, and patient-reported outcome measures were also similar, suggesting that rehabilitation might be as effective as prehabilitation.

### **Frailty**

In medical terms, frailty is not an illness, but a syndrome that combines the effects of natural ageing with the outcomes of multiple long-term conditions, and a loss of fitness,

strength, and physiological reserves. When compared with a robust state, frailty is characterised by greater vulnerability to stressors, and impaired recovery from them. Patients with frailty may have reduced motility, muscle weakness, sarcopenia, poor balance, deficits in motor processing, cognitive decline, weight loss and limitation of activity with reduced endurance and stamina.<sup>28</sup> Reduced mental and physical resilience means that a relatively 'minor' postoperative complication can have a severe long-term impact on health and wellbeing.

Even in the absence of complications there is a 20-40% reduction in postoperative physical function and a deterioration in quality of life after major surgery in older adults.<sup>29</sup>

Intuitively, patients with frailty are more likely to benefit from prehabilitation than those who are fit, but this depends on their ability and motivation to undergo exercise training. However, a randomised clinical trial that allocated 144 patients above the age of 70 years with or without American Society of Anesthesiologists physical status 3 or 4 to receive either standard care or standard care plus a motivational interview, high-intensity endurance training and promotion of physical activity showed that the intervention group had a 51% reduction in the number of patients developing postoperative complications.<sup>10</sup>

### **Meta-analyses**

Three meta-analyses have shown that although prehabilitation reduced postoperative complications, there was no effect on length of hospital stay,<sup>21, 30, 31</sup> and one showed that although there was no reduction in complication rates, patients who received prehabilitation had a shorter length of stay.<sup>11</sup> A recent systematic review identified 178



randomised clinical trials involving eight different types of prehabilitation interventions, but only 3 to 18 of these trials could be included in the meta-analyses, highlighting heterogeneity of populations and interventions, as well as the difficulty in comparing data across trials.<sup>12</sup> The authors concluded that although some prehabilitation interventions might reduce postoperative complications and length of stay, the quality of the evidence is low.<sup>12</sup> None of the interventions had an effect on mortality. While immune modulating nutrition, inspiratory muscle training and multimodal prehabilitation reduced length of stay, incentive spirometry, psychological support, oral nutritional supplements, education and weight loss had no significant effect. A recent umbrella review of 55 systematic reviews showed that low certainty evidence suggests that prehabilitation might improve postoperative outcomes.<sup>32</sup>

The fact that multimodal interventions have a greater magnitude of effect than individual interventions exemplifies the marginal gains theory, popularised in the sport of cycling and advocated in aviation, business, and even healthcare.<sup>22, 33</sup> The cumulative effect of marginal gains could result in substantial benefits for the individual patient undergoing major surgery. This undoubtedly provokes the question of whether or not, unimodal intervention studies should be undertaken in isolation or in combination with other interventions to exploit the potential benefits of marginal gains.

### **Cancer surgery and prehabilitation**

Surgery is the mainstay of treatment for most cancers, and both clinicians and patients feel that there should be a certain expediency, with cancer treatment being time sensitive from

the clinical, emotional and healthcare targets points of view. A recent systematic review has shown a significant association between delay in cancer treatment and increased mortality for seven different cancer types.<sup>34</sup> Increased mortality risk for each 4-week delay ranged from 1.06-1.08 (95% CI 1.01 to 1.13) for cancers primarily treated with surgery.<sup>34</sup> However, some patients with cancer have underlying inflammation, sarcopenia and even sarcopenic obesity. Performing surgery on unprepared patients with these conditions could result in major complications and even mortality. While prehabilitation is unlikely to reduce obesity or improve sarcopenia, it is likely to improve metabolic flexibility. Prolonged periods of prehabilitation, 12 weeks as suggested initially,<sup>4</sup> may delay surgery and negate the benefits because of tumour progression. Equally, inadequate prehabilitation is unlikely to be of benefit. Nevertheless, if prehabilitation can be shown to reduce complications of cancer treatment it may have a benefit on quality of recovery, quality of life and the ability to complete adjuvant therapy, particularly if the waiting period for surgery is leveraged without a delay in surgery.<sup>35</sup>

Surgery for oesophagogastric, rectal and some pancreatic cancers is often preceded by several weeks of neoadjuvant chemotherapy or chemoradiotherapy and this provides an opportunity for a natural experiment on the benefits of prehabilitation.<sup>35</sup> A recent trial randomised patients with locally advanced oesophagogastric cancer to receive prehabilitation (n=26) or standard care (n=28). The 15-week prehabilitation programme comprised twice-weekly supervised exercises, thrice-weekly home exercises, and psychological coaching.<sup>9</sup> Although no difference between groups was noted in anaerobic threshold (the primary end-point), after completion of neoadjuvant therapy, the multimodal prehabilitation group showed significant improvements in peak VO<sub>2</sub>, handgrip strength,

global health status and weekly step counts.<sup>9</sup> However, there was no difference in outcome between groups when clinically relevant measures such as length of stay, complications, 30-day readmissions, and 30-day, 90-day and 3-year mortality were considered.<sup>9</sup>

### **Potential risks of prehabilitation**

Cardiopulmonary exercise testing (CPET) has been used to ascertain the fitness of patients for major surgery and is often a prelude to prehabilitation. The intensity of the exercise is increased gradually during the test until the individual is unable to continue. In a large multicentre study of 1401 patients undergoing CPET prior to surgery, there were 71 (5%) patients with a rise or fall in arterial pressure, 25 (2%) with ischaemic cardiac events, 3 with syncope, and 2 with chest pain.<sup>36</sup> As prehabilitation does not reach the level of exertion attained during CPET, the incidence of adverse events is expected to be low. No adverse events were observed in surgical patients who exercised on a stepper for 30 min<sup>15</sup> or performed moderate intensity cycling for 25 min.<sup>9</sup> Other studies on prehabilitation,<sup>13, 16, 17</sup> including one involving HIIT,<sup>10</sup> did not report adverse events.

### **Cost**

The costs of prehabilitation vary according to the regimens used, duration and setting, and have been estimated to be between \$300-400 per patient.<sup>37, 38</sup> However, these do not include societal costs such as transportation, exercise equipment, gym membership and expenses incurred by accompanying carers. There are no systematic reviews on the cost

savings of multimodal prehabilitation. A modelling study has determined that the average price of preoperative optimization could be as high as \$6421 per patient without affecting its cost effectiveness<sup>39</sup> and another modelling study found that prehabilitation remained cost effective over a year up to a cost of intervention of \$9,418 per patient.<sup>38</sup> Nevertheless, in a randomised clinical trial of trimodal prehabilitation there were no statistically significant cost savings at 30 days.<sup>37</sup> Additionally, no differences in costs were found when stratifying by level of surgical aggression or surgical risk.<sup>37</sup>

Appropriate patient selection is of utmost importance in low- and middle-income countries (LMICs) where healthcare systems are significantly burdened by the high cost of complex prehabilitation programmes.<sup>13</sup> Reduction of sedentary behaviours at home and promotion of physical activity prior to surgery could help implement prehabilitation in LMICs without recourse to sophisticated equipment. Community-based rehabilitation programmes could be effective in increasing adherence while reducing overall costs. The use of online exercise sessions fits with the NHS initiative, which states that the health system should promote digitisation, telemedicine, and the integration of technologies such as virtual reality.<sup>40</sup>

### **Limitations of the evidence**

The results of randomised clinical trials and meta-analyses on prehabilitation are variable, and the strength of the published evidence is relatively weak. Heterogeneity of patient populations, interventions and outcome measures, as well as relatively small sample sizes and inclusion of low-risk populations can contribute to bias.<sup>12</sup> Prehabilitation regimens have been largely unsupervised and compliance with the proposed interventions has varied

from 16% to 97%,<sup>41</sup> while some studies do not report compliance at all. A recent feasibility trial showed that 84 of 198 patients (42%) approached were deemed ineligible for prehabilitation because of time constraints and that only 22 (18%) finally consented to recruitment, thereby limiting generalisability.<sup>42</sup> Exercise-based interventions were used as controls in some studies<sup>15</sup> and there has been a lack of individualised regimens tailored to patient abilities. Given the nature of the intervention, blinding has not been possible and only few studies report the combined effect of enhanced recovery after surgery regimens and prehabilitation. Increasing aerobic capacity by prehabilitation may not be a direct mechanism to reduce surgical complications – it is simply a marker of effective exercise intervention that has altered metabolic function, e.g., improved metabolic flexibility by exercise intervention.

## **Conclusions**

Considerable research effort is required to identify the distinct processes and mechanisms that contribute to effective prehabilitation and post-surgical recovery interventions.

Perhaps, the evidence can be strengthened by the conduct of large scale, appropriately powered multicentre trials that have unequivocal clinically relevant and patient-centric end points.<sup>43</sup> Complications, hospital stay and mortality, quality of recovery, quality of life and cost effectiveness should be included as outcomes. Completion of adjuvant therapies and long-term survival should also be recorded in patients with cancer. Researchers should concentrate on recruiting patients who are frail and at high-risk. Interventions should be multimodal and exercise regimens should be tailored to patient ability. The latter may

necessitate involvement of patient focus groups and patient feedback. Compliance should be recorded and ideally, exercise sessions should be supervised, either in person or virtually. Exercise and nutritional interventions should also be tested in the postoperative rehabilitation period.

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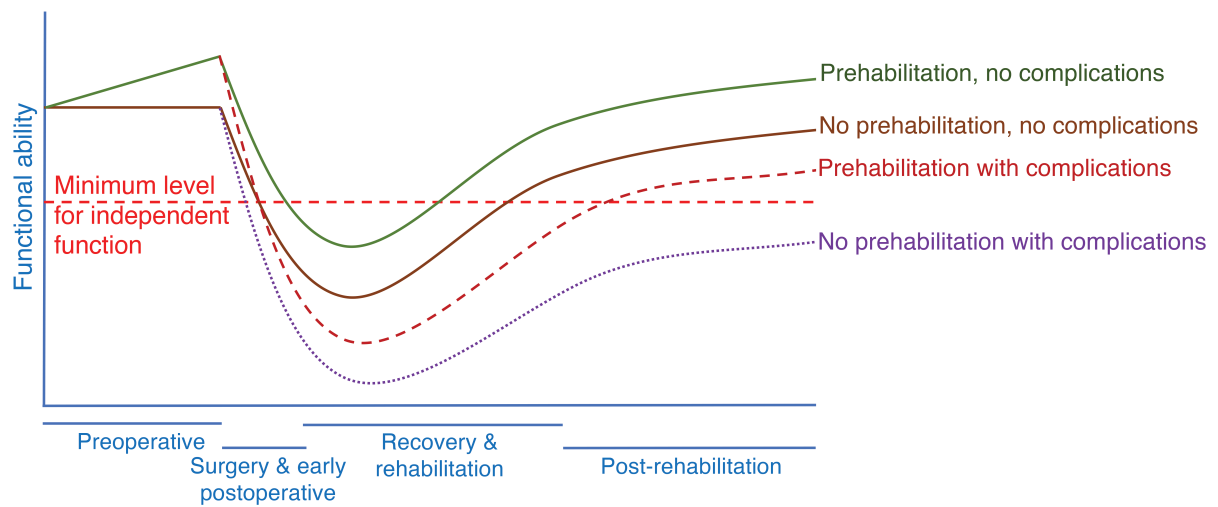
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**Figure**



**Figure 1:** Potential advantages of prehabilitation (modified from Carli and colleagues<sup>4</sup> and Durrand and colleagues<sup>7</sup>)