Prehabilitation as an Integral Procedure in Predictive, Preventive, and Personalized Medicine and Modern and Effective Healthcare

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Abbreviations

5A's	Ask, Advise, Assess, Assist, Arrange
6MWT	6-min walk test
AAR	Abbreviated variation of the 5A's—Ask, Assist, Refer
BJA	British journal of anesthesia
BMI	Body Mass Index
CI	Confidence interval
DrEaMing	Drinking eating and mobilizing
DRM	Disease-related malnutrition
ERAS	Enhanced recovery after surgery
ESPEN	European Society for Clinical Nutrition and Metabolism

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FFMI	Fat-free mass index
FITT	F—frequency, I—intensity, T—time, T—type
HR	Hazard ratio
IGF	Insulin-like growth factor
PPPM/3 PM	Predictive, preventive and personalized medicine
SD	Standard deviation
SF-36	36-item short form health survey
SHS	Suboptimal health state
TCAM	Traditional complementary and alternative medicine
TUG	Timed up-and-go

1 Introduction

1.1 History of Prehabilitation

One of the first use of the term "prehabilitation" can be traced back to the beginning of 1940s of the twentieth century [1]. Originally it was understood as the procedure dedicated to solve health-related problems prior to the recruitment or prior to the unwanted manifestation during a military operation. In parallel, the pre-placement examinations of the employees in the industry were introduced by W.A. Sawyer in 1942 [2].

Later on, in 1952, in the German journal, the term "preoperative" is used in relation to the preoperative breathing exercise in thoracic surgery [3].

In the beginning of the 1980s the meaning of the "prehabilitation" changed and it is now defined as "the process of expanding patient's functional and psychological capacity to reduce potential deleterious effects of a significant stressor, which is the surgical procedure itself" [4]. The Cambridge dictionary defines "prehabilitation" in medical context as "activities done by someone before they have a medical operation in order to improve their physical strength and help them to recover more quickly after the operation" [5]. According to the BJA Education journal, prehabilitation is "the practice of enhancing a patient's functional capacity before surgery, with the aim of improving postoperative outcomes" [6]. The Collins dictionary defines "prehabilitation" as "the preparation of patients prior to major surgical procedures to enhance general

health and well-being with the outcome of decreasing morbidity and mortality" [7].

Prehabilitation has also been defined as "a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments" [8].

Nowadays, in principle, every definition of "prehabilitation" is in primary connection with surgery. When we take a closer look at this topic, we come to the conclusion that "prehabilitation" is an important part of the majority of medical protocols dedicated to the best preparation of the patient for the particular medical procedure. As an example we may take cancer treatment—chemotherapy, radiotherapy and hormonal treatment, can, undoubtedly, have a negative impact on health or the functionality of the organs [9]. Poor physical condition and poor, or inappropriate, dietary habits have been identified as important reasons for low adherence to neo-adjuvant treatment resulting in an inability to respond to it, while it is known that the more late adjuvant treatment starts as result of poor physical condition, the higher is the mortality [10].

Clearly, knowing the growing field of PPPM/3 PM, prehabilitation can, and should, use all accumulated and published scientific knowledge, technologies and tools, including research into the suboptimal health status [11] of a specific patient who is to go through scheduled therapeutic/surgical procedure, result of which depends on the patient's specific health status. In our opinion, this condition should be assessed using available medical technologies in order to predict potential problems and to prevent them with adequate preventive measures, whether it is personalized nutritional support based on a biochemical analysis of the patient's blood and other biological samples, specific physical exercises to increase fitness, psychological support, disease-related patient education about scheduled disease or procedure, chronic pain prediction, assessment of mitochondrial health and function, as discussed in another chapter of this book, as well as identification of negative environmental factors that need to be suppressed and health-supporting environmental factors that need to be enhanced in all relevant fields like obstetrics, oncology, organ transplantation, surgery, dental care, neurodegenerative diseases, genetic diseases, pandemic management and other areas of healthcare (Fig. 1).

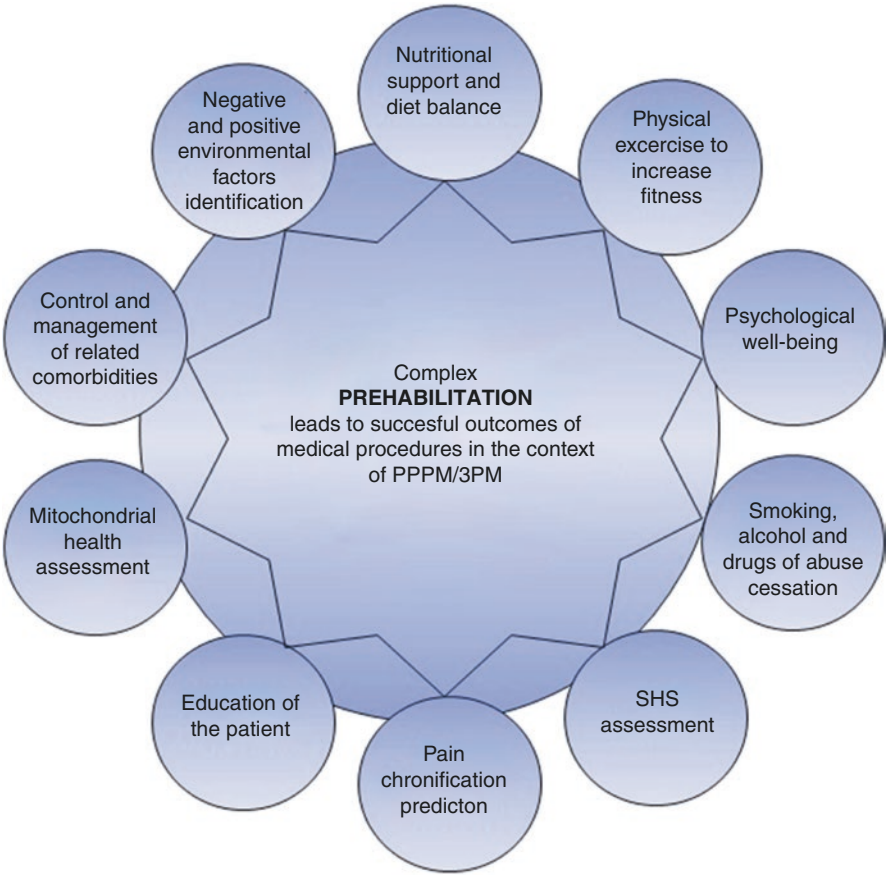

Fig. 1 Complex prehabilitation in the context of PPPM/3 PM should be multimodal and include also other health-supporting activities apart of the standard ones which are nutrition, physical activity, psychological well-being, smoking cessation, and control of related comorbidities. Here we suggest enhancing the process of prehabilitation with inclusion of particular questionnaires focused on identification of suboptimal health state (SHS), pain chronification prediction, mitochondrial health assessment, cessation of smoking, alcohol consumption and drugs of abuse, particular health-problem-related education of the patient, control and management of related comorbidities, and identification of environmental factors having negative influence on health and worsening disease state, or on the contrary, having positive influence on health which may increase the chances for better outcome of the desired medical procedure and speed up the consequent recovery. Providing, of course, that the particular medical procedure is not provided under an emergency situation when there is no time for complex prehabilitation as outlined in this figure

2 Prehabilitation

2.1 Multimodal Approach of Prehabilitation

Prehabilitation requires a well-designed approach from several disciplines, the so-called multi-modal prehabilitation, requiring a fundamental change of the current medical care paradigm [12].

Although this is a long-term vision, we suggest initially focusing on patients at high risk of postoperative morbidity and mortality, such as elderly surgical patients who are weak (frail) and unprepared for the significant burden of a particular procedure [13, 14]. In the later stages of the implementation of prehabilitation processes, as already suggested by several researchers [15], the hospital should offer prehabilitation for a much wider spectrum of patients and, as we believe, also for other than surgical patients who need specific medical procedures.

The basis of any multimodal prehabilitation approach (exercise and adequate physical activity, nutrition improvement and adjustment, psychological support and well-being, patient education, etc.) is a personalized intervention with the possibility of prediction, which prevents negative clinical outcomes.

From the point of view of rapid recovery after a given surgical or other medical procedure, and from the point of view of regaining physical strength, prehabilitation has the potential to increase the chances of returning home earlier and to engage in the usual activities that were performed before the undertaken procedure. Last but not least, it is also expected that supported and accelerated recovery will have an impact on the economy, effectiveness and utilization of beds available in hospitals, as well as on the use of limited financial resources in the health care system in any country worldwide [12].

The following are the basic elements of prehabilitation:

- Physical training through exercise.
- Nutritional support and supplementation.
- Mental support, patient education, and patient empowerment.
- Cessation of smoking and behavioral changes.
- Control of related comorbidities.

2.1.1 The Reason for Multimodal Approach in Prehabilitation

Exercise without nutrition will not increase muscle mass. Nutrition is better utilized in combination with training. For training a good mental state is mandatory and on the other hand the effort of training will be rewarding for your mental state. Moreover, ultimate goal is to generate persistent behavioral changes through all elements [16].

In one randomized trial, 77 patients undergoing colorectal resection for cancer received a home-based intervention consisting of moderate aerobic and resistance exercises, as well as nutritional counseling with protein supplementation and relaxation exercises, beginning either 4 weeks before surgery (prehabilitation group), or immediately after hospital discharge (control group). Both groups continued the regimen for 8 postoperative weeks. The primary functional capacity outcome was the 6-min walk test. Better 8 week 6-min walk test scores were noted in the prehabilitation group (+23.7 with standard deviation (SD) 54.8 m versus −21.8 with SD 80.7 m, with a mean difference of 45.4 m (95% CI 13.9–77.0)). Also, a higher proportion of patients in the prehabilitation group recovered to an exercise capacity greater than their baseline at 8 postoperative weeks (84 vs. 62%) [17].

Similar interventions and improvements were noted in another randomized trial of prehabilitation before colorectal cancer surgery with additional supervised exercise sessions during the first three postoperative days [18]. In a meta-analysis that

included these two randomized trials together with one prospective cohort study [19], multimodal plus nutritional prehabilitation was associated with improved disease-free survival 5 years after colorectal cancer surgery (hazard ratio (HR) 0.45, 95% CI 0.21–0.93; 202 total patients) [15, 20].

One international multicenter, randomized controlled trial with two study groups (714 patients) in progress, with inclusion of four prehabilitation interventions (in-hospital high-intensity endurance and strength training, high-protein nutrition supplementation, smoking cessation, and psychological support) [21] have as primary outcomes postoperative complications (assessed with the Comprehensive Complication Index [22]) at the 30 days of follow-up and functional capacity (assessed with the 6 min walk test) measured 4 weeks after surgery and compared to baseline and additionally directly after prehabilitation and 8 weeks after surgery. Notably, 86% of patients in the prehabilitation group recovered baseline functional capacity within four postoperative weeks compared with 40% in the control group [15, 21]. The authors concluded that prehabilitation programs are feasible, effective, and safe [15].

Research on prehabilitation has focused primarily on patients undergoing elective cardiac surgery [15, 23], and major gastrointestinal or hepatobiliary cancer surgery [15, 20, 21]. In some centers, patients undergoing other types of major surgery are candidates for prehabilitation, such as those undergoing joint replacement surgery [15, 24–26] or major vascular surgery [15, 27]. Some authors, however, propose offering prehabilitation for all surgical patients [15].

In the context of the implementing PPPM principles within hospital health care processes [28], we suggest that prehabilitation be included in standard therapeutic procedures in every hospital that wants to improve the level of care provided and thus apply PPPM in routine practice, which will certainly benefit patients. We are aware that the practical implementation of this vision will not be easy but we are also sure that the well-organized cooperation of all interested parties, including those at the international level, who want to change the current disease-oriented philosophy to future healthcare, oriented to prediction, prevention and a personalized approach can accelerate beneficial changes.

2.2 Exercise and Physical Activity (Rehabilitation) as Element of Prehabilitation

In the last decade, there has been a growing awareness that the success of treatment itself depends not only on technical surgical skills, radiation therapy, and targeted therapy, but also on the patient's overall physical and mental condition [29]. At present, the purpose of treatment for patients is to shorten hospital stays, to release patients who are relatively self-sufficient, in good physical condition, to home care, and then to work to improve the patient's functional status [30]. In medical terminology, this continuous care process in the cancer patient, which is provided since cancer diagnosis, and also includes nutritional support, support of physical and mental health to reduce the incidence and severity of future complications, can be called prehabilitation [31].

Personalized treatment of any disease, especially cancer, is indeed a major challenge. Exercise without nutrition will not increase muscle mass, and, on the other hand, nutrition is better utilized in combination with adequate training. A good mental state is mandatory for training, and in return the effort of training will be rewarding for patient's mental state [16]. Therefore, rehabilitation is an essential part of prehabilition but cannot be confused with prehabilitation itself. Rehabilitation is a potentially effective strategy to improve the functional status and quality of life of patients [32]. Exercise interventions are known to alleviate or prevent the deleterious effects of cancer and treatment [33]. Rehabilitation provides also an opportunity to improve the health care of cancer patients [33]. The evidence for exercise in the care of cancer patients is largely positive.

Rehabilitation includes a complex process that improves the course of the disease, reduces the functional impairment, accelerates the reconvalescence of the patient and faster return to the family and working environment [34]. Patient rehabilitation is focused on restoring functional state and integration of the patient into society [35]. The complexity of the prehabilitation and rehabilitation processes is given by the fact that the patient is understood as a person who may have both physical and mental difficulties. In more serious cases, these impairments are associated with damage to work potential and disability. Due to the increasing number of surviving colorectal cancer patients, there is a growing need for an effective program before, during, and after treatment [36]. Rehabilitation is one of the basic components of treatment to improve the health of a patient [37]. Basic rehabilitation therapies include exercise [38]. The purpose of prehabilitation is to achieve maximum benefit in terms of improving the functional and mental state of the patient [39]. Physical activity plays an important role for the cardiovascular system and muscle function and mass maintenance, which are critical factors for the postoperative recovery of a patient [40].

Physical performance of patients is a multidimensional concept that involves body function related to movement. Exercise, together with other components of prehabilitation plays an important protective and therapeutic role in patients with colorectal cancer [33]. Although the link between exercise and the prevention of colorectal cancer appears clear, the molecular mechanism underlying the protective effect of exercise is not yet clear [41]. The link between the protective and therapeutic benefits of exercise and cancer can be explained by several mechanisms. These mechanisms include an explanation for metabolic dysregulation, which includes the effect of exercise on insulin resistance, glucose metabolism, and insulin-like growth factor (IGF) [42]. Physical activity reduces insulin resistance and insulin levels affecting the IGF pathway and indirectly reduces the risk of colorectal cancer, recurrence, and mortality [43]. Another significant effect of exercise is the effect on adiposity, which includes, in particular, the effect on leptin and adinopectin [44]. Another possible explanation is the effect on oxidative stress, inflammation, and impaired immune function. Another important effect is the effect of exercise on myokines and interleukins [45].

Current recommendations for physical activity and exercise in prehabilitation include 150 min of moderate or 75 min of vigorous physical activity per week. Exercise prescription should follow the FITT principles:

F—frequency (how often).
I—intensity (how hard).
T—time (how long).
T—type (what kind of exercise).

The recommendations for exercise are based on the guideline of 150 min per week, aerobic training should occur at least every second day for 30–45 min, in duration at a moderate level of intensity (50–75% of age predicted maximum heart rate). The exercise itself may be of different type—aerobic component, resistance, flexibility, balance exercises. It must be tailored to suit the needs and physiological status of each patient and designed and supervised by qualified personnel.

Even for the patient who is unable or does not want to embark on training program, health benefits can still be acquired by increasing activities of daily living—light walk, stair climbing, gardening, housework, dancing, swimming, hiking, biking [12].

2.2.1 Patient Examination and Setting Up Training in Terms of Prehabilitation

The effectiveness of rehabilitation depends on a comprehensive and interdisciplinary approach [46]. Current procedures emphasize rehabilitation as an important part of surgical treatment [47]. There is growing evidence for the benefits of rehabilitation in various cancers [48–51]. The rehabilitation model currently focuses on optimizing treatment for cancer patients. Rehabilitation is a complex model and its mutual integration into the health system represents a potential benefit for patients. Most patients have reduced function. Functional examination plays an important role in rehabilitation, where it is possible to use several functional examinations.

2.2.2 6-Minute Walk Test

The 6-min walk test is a submaximal exercise test used to assess aerobic capacity and endurance in various pathological conditions [52]. The distance traveled in 6 min is used as a result to compare changes in functional capacity in patients. This test can be used in patients of all ages. The test was originally designed to help evaluate a patient with cardiopulmonary problems. It was gradually introduced into other diagnoses [53]. It also plays an important role in the examination of colorectal cancer with respect to the functional fitness of patients [54]. The 6-min walk test gives information on the patient's functional capacity and provides important information on all systems during physical activity, including the pulmonary and cardiovascular systems. To perform the test, it is necessary to measure the range in which patients will perform the test.

2.2.3 Chair Stand Test

The chair stand test is a test for testing the strength and endurance of the legs in older adults [55]. It is part of a senior functional test battery. The chair stand test evaluates the functional strength of the lower limbs, balance, and the risk of falling

in older adults. The evaluation of the test is based on the amount of time. During the test, the patient sits in a standing and sitting chair five times. A stopwatch and a standard height chair with a straight back are important to perform the test. If the test is performed correctly, the patient sits with a straight back and is supported. The patient is also instructed to rest his hands on his chest and then sit down and rise five times as quickly as possible. The shorter the time to complete the test, the better the indicator of the test result.

2.2.4 Timed Up-and-Go Test (TUG)

This test is mainly used in the elderly population. TUG focuses on the functional ability of patients and the assessment of fall risk [56]. In patients with colorectal cancer, it can represent a benefit in determining the physical impairment caused by colorectal cancer [56]. A stool and stopwatch are required to perform the test. The patient sits in a chair to perform the test correctly. His feet are placed in place marked by a line. After the start signal, the patient gets up from the chair and walks a distance of 3 m. The clinician records the time the patient walked the specified distance and returned to the stool.

2.2.5 SF36 Quality of Life Questionnaire

The quality of life questionnaire was created on the basis of the requirement of adequate evaluation of therapies in medicine. The SF36 questionnaire is a standardized form to evaluate patient quality of life [57]. SF36 contains 36 questions, the results of which are scored. SF36 addresses a set of general, coherent, and easy-to-apply questions about patients' quality of life.

Two types of exercise are most often used in the rehabilitation of patients. It is resistance exercise and aerobic exercise.

2.2.6 Resistance Training

Resistance exercise using resistance to stimulate muscle contraction. It is important to maintain a slow controlled movement during strength training. During strength training, it is possible to increase the load due to the patient's health. Strength training consisting of concentric and eccentric muscle contraction is a safe, simple, and effective intervention to induce muscle hypertrophy, increase muscle strength, and improve the patient's functional condition before and after surgery/medical procedure.

2.2.7 Aerobic Exercise

This type of physical activity is one of the most common. During aerobic training, the patient exercises at a moderate load intensity. Aerobic exercise is known to induce an increase in skeletal muscle mitochondria. Muscle mitochondrial cells are able to adapt to aerobic training. Aerobic exercise begins with warming up in the form of 10 min of light activity and dynamic stretching. As a form of aerobic exercise it is possible to use walking, Nordic walking, swimming, cycling. Exercises focused on the aerobic component in patients are applied twice a week.

2.2.8 Respiratory Exercises

Respiratory rehabilitation is a therapy for patients with symptoms related to impaired lung function. It has been started in patients with chronic obstructive pulmonary disease. It is a standard treatment for patients with lung cancer. Respiratory rehabilitation is aimed at improving the physical and mental condition of the patient. The primary purpose of respiratory rehabilitation is to improve the patient's physical function, functional condition, and quality of life.

2.2.9 Goals of Physical Activity as Element of Prehabilitation

- To identify patients with poor physical conditioning (6MWT, cardiopulmonary exercise testing).
- To prescribe a targeted and individualized exercise program (cardiovascular, resistance, flexibility, balance training).
- To encourage daily physical activity that totals at least 30 min per day.
- To reduce sitting or sedentary time.
- To change long term behavior to include a more active lifestyle [12].

2.3 Nutritional Optimization, Nutritional Balance as Elements of Prehabilitation

The rate of development of postoperative malnutrition for a given individual depends upon their preexisting nutritional status before the surgery, the nature and complexity of the surgical procedure, the degree of postoperative hypermetabolism, and their ability to consume an optimal number of calories [58]. Starvation during metabolic stress from any type of injury differs from fasting under physiological conditions [59].

The stress of surgery or trauma creates a catabolic state, increasing protein and energy utilization. Macronutrients (fat, protein, and glycogen) from the labile reserves of fat tissue and skeletal muscle are redistributed to more metabolically active tissues such as the liver and visceral organs. This response can lead to the onset of protein calorie malnutrition (defined as a negative balance of 100 g of nitrogen and 10,000 kcal) within a few days [58, 60–62].

Definitions of malnutrition often include an "unbalanced nutritional state" that leads to "alterations in body composition" and "diminished function" [63]. An unbalanced nutritional state refers to both over- and undernutrition [64].

With an increasing percentage of obese people in the Western world is malnutrition often not realized and Disease-related Malnutrition (DRM) frequently not recognized and therefore untreated [65].

According to ESPEN (European Society for Clinical Nutrition and Metabolism) diagnostic criteria for malnutrition according to two options [65].

- option 1: BMI <18.5 kg/m^2,
- option 2: combined: weight loss >10% or > 5% over 3 months and reduced BMI or a low fat-free mass index (FFMI).

Reduced BMI is <20 or < 22 kg/m^2 in patients younger and older than 70 years, respectively. Low FFMI is <15 and < 17 kg/m^2 in females and males, respectively.

From the prehabilitation point of view it is important to note that nearly 50% of patients admitted to hospital are malnourished or at risk of malnutrition [66]. The American Society for Enhanced Recovery and Perioperative Quality estimates that two out of three patients undergoing gastrointestinal surgery are malnourished, which renders them three times more likely to suffer perioperative complications and five times more likely to die [67].

Malnutrition is associated with a poorer response to cancer treatment [68], increased susceptibility to infection, poor wound healing, increased frequency of decubitus ulcers, overgrowth of bacteria in the gastrointestinal tract, abnormal nutrient losses through the stool [58, 69–71] and hypoalbuminemia is associated with post-surgical mortality, increased morbidity and length of stay [68].

Perioperative nutritional supplementation has been shown in a recent meta-analysis of 56 trials including 6370 patients to decrease postoperative infectious and non-infectious complications, and also length of stay in patients undergoing gastrointestinal cancer surgery [72, 73].

2.3.1 Synergy Between Feeding and Exercise

Speaking of nutrition, we have to emphasize the fact that lean tissue accretion will not occur without a positive protein balance, with protein synthesis exceeding protein breakdown. Stable isotope studies suggest net muscle protein balance postexercise remains negative until amino acids are available [74–76]. It is the synergistic effect of feeding- and exercise-induced stimulation of muscle protein synthesis that positively impacts protein balance, to a greater extent than either feeding or exercise could alone. Repeated bouts of resistance exercise and protein feeding stimulate lean tissue gains which is essential for a better and quicker recovery after surgery and a healthier life [74, 75]. It is important to keep in mind that for training a good mental state is mandatory.

2.3.2 Goals of Nutritional Optimization as Element of Prehabilitation

- To identify patients who are malnourished.
- To better understand how the patient is eating and to identify where deficiencies are occurring.
- To provide feedback as to how the patient can optimize their nutrition.
- To provide appropriate nutritional supplementation [12].
- Minimize starvation.
- Prevent pre and postoperative malnutrition.
- Support anabolism for recovery [65].
- Although additional nutritional considerations will be required for surgical subspecialities and to provide personalized patient care, these basic nutrition principles hold true for all cases [74].
- In addition, given the rising proportion of cancer patients who are obese at diagnosis, the prehabilitative window and rehabilitative window are potentially an opportunity to embed new lifestyle behaviors [68].

2.4 Psychological Well-Being as Element of Prehabilitation

Preoperative anxiety, depression and low self-efficacy are consistently associated with worse physiological surgical outcomes and postoperative quality of life. This has led to the emergence of psychological prehabilitation and the trimodal approach to prehabilitation, incorporating psychological intervention as well as exercise and nutritional optimization [77].

2.4.1 The Reasons for Psychological Well-Being as a Part of Prehabilitation

Increasingly, evidence suggests that psychological factors have an impact on both physiological and psychological surgical outcomes in the short as well as long term [77].

A systematic research identified 16 eligible studies summarized the association between psychological factors and physiological outcomes affecting the site of surgery, namely wound healing and postoperative complications in the first month after surgery. However, there was significant heterogeneity across the studies, overall, trait and state anxiety, state anger, active coping, subclinical depression, and intramarital hostility appeared to complicate recovery, while dispositional optimism, religiousness, anger control, low pain expectations, and external locus of control seemed to promote healing. Psychological interventions (guided relaxation, couple support visit, and psychiatric interview) also appeared to favor recovery. Psychological factors unrelated to surgical outcomes included loneliness, perceived social support, anger expression, and trait anger [78].

Another review with inclusion of 29 studies evaluated the effect of mood, attitudinal factors, personality and coping mechanisms on complications, pain and analgesic use, functional recovery, length of hospital stay and ratings of physical recovery [79].

Psychological factors can also affect both acute and chronic postoperative pain [77]. Anxiety is one of the four factors that predict acute postoperative pain as was identified in qualitative systematic review including 48 trials and 23,037 patients [80] and there is a high level of evidence for the predictive value of pre-surgical depression, psychological vulnerability and chronic stress on the risk of chronic pain after surgery [81].

2.4.2 The Ways to Achieving Mental Well-Being in Terms of Prehabilitation

A recent Cochrane review of 105 studies from all surgical specialties synthesized the evidence of psychological preparation and postoperative outcomes of pain, return to normal activities (behavioral recovery), length of hospital stay and negative effect in adults undergoing elective surgery. They evaluated a broad range of psychological interventions including: procedural information (information about what, when and how processes will happen); sensory information (what the experience will feel like and what other sensations they may have, for example, taste, smell); behavioral instruction (telling patients what they need to do); cognitive

intervention (techniques that aim to change how people think); relaxation techniques; hypnosis; and emotion-focused interventions (techniques that aim to help people to manage their feeling) [77, 82]. Such interventions should be proposed as preoperative education programs [77].

2.4.3 Goals of Psychological Well-Being as Element of Prehabilitation

- To identify patients who require psychological interventions.
  To provide anxiety reducing techniques for all patients, based on preference [12].

2.5 Pain Management in Prehabilitation

As we discuss in another chapter of this book dedicated to pain chronification prediction and to the reasons for including its assessment into the processes of prehabilitation in context of PPPM/3 PM, psychological factors affect pain perception in a fundamental way. Pain is a complex, multidimensional perception with a diversity of its quality, intensity, duration, location, as well as perception of its discomfort, while the intensity and degree of discomfort of pain are not directly dependent on the cause and extent of tissue damage. In particular, situational and emotional psychological factors present in the experience of pain can fundamentally change the intensity and quality of pain perception. As the pain suddenly reaches the brain, the thalamus redirects its feelings to other cortical and subcortical parts of the Pain matrix, which are also associated with emotions, attention, and memory. This explains why emotions have such an effect on how we feel [83].

Every chronic pain develops from acute pain. The onset of acute pain is associated with tissue damage through various mechanisms (e.g., mechanical damage, burns, infection, inflammation, genetic disorders, etc.) and thus the integrity of the biological structures and functions of the individual. Therefore, fear (= the first affective phase of pain) and anxiety of its persistence are naturally associated with its occurrence. For the patient's adaptation to pain and further development of the painful state, his/her current attitude is essential to actual acute pain. Thus, it is essentially a question of whether he/she accepts it as a positive and necessary signal, or succumbs to the fear of pain and, by excessive obsession and catastrophe, neurotizes its further development and thus creates the conditions for neural sensitization and pain chronification. This creates a gradually deepening suffering, which is a complex of negative affective and cognitive processes. The affective component of suffering is characterized by anxiety, anger, and depression (= second affective phase of pain), the cognitive component of suffering includes views on pain and its impact on the sufferer, most often devaluing his whole life and perception of the environment [84].

In addition to the evidence describing the importance of psychological factors on physiological outcomes after surgery, emerging data suggest psychological state before cancer surgery may have an impact on longer term quality of life and well-being [77]. Higher pre-surgical depression and lower self-efficacy to manage illness

were significantly associated with poorer trajectories of recovery [85]. Within the field of oncology, an emphasis on reductions in stress and anxiety are emerging increasingly [77].

Therefore we suggest that pain chronification prediction should be included in the process of prehabilitation as a part of practical implementation of PPPM/3 PM in the routine processes of future healthcare, as we discuss in more details in the dedicated chapter of this book (see also Fig. 1).

2.6 Smoking and Other Cessations as Element of Prehabilitation

Patients should be strongly encouraged to cease smoking as part of any prehabilitation program [86]. The perioperative period is considered to be a "teachable moment" when the need for surgery might serve as a driver for permanent behavioral changes including smoking cessation [86–88]. Cigarette smoking is a risk factor for several perioperative pulmonary, cardiovascular, and wound healing complications. Limited evidence suggests that risks are also associated with "vaping" (i.e., use of electronic cigarettes [e-cigarettes]) as a method for consumption of nicotine (or other substances such as cannabis) [89]. Smoking increases the risk of postoperative morbidity and mortality. Smoking cessation before surgery reduces the risk of complications [86].

2.6.1 The Way to Cease Smoking in Terms of Prehabilitation

One of the possible way is "The 5A's" (**Ask** about tobacco use, **Advise** quitting, **Assess** readiness to quit, **Assist** smokers ready to quit, **Arrange** follow-up) or abbreviated variation "AAR" (**Ask** about tobacco use, **Assist**—Offer advice to quit and assistance to make a plan, including prescribing cessation medication, **Refer** to behavioral support resources to continue treatment after the visit) [90–92].

At this point we have to essentially emphasize that, logically, it is not only the cessation of smoking that is important, although it is the most pronounced one within the standard elements of prehabilitation, but also cessation of body intoxication from other resources such as, for example, alcohol, drugs of abuse, environment, food, beverages, is important from the perspective of more complex prehabilitation under the changed paradigm of healthcare brought by PPPM/3 PM.

2.7 Importance of Prehabilitation Before Major Surgery in Context of PPPM

Successful surgery does not depend exclusively on the procedure alone but, rather, on how quickly and efficiently the patient can return to his normal life. With increasing awareness of ERAS (Enhanced Recovery After Surgery) protocols, prehabilitation as an integral part of preoperative period takes on larger dimensions.

Improving preoperative functional capacity together with following best-evidence practice medicine, may be a tool to safely and effectively raise the number of patients suitable for curative-intent surgical procedures [12].

It follows from the above mentioned that a successful operation depends on a combination of technical surgical skills and, on the other hand, also on metabolic interventional therapy "tailored" to the patient's metabolic status. This includes providing appropriate nutritional, physical and psychological support. Suitable perioperative management may be vital for long-term outcome in oncology patients [93, 94]. Half of the patients still manifest a degree of incapacity 3 months after major elective abdominal surgery [95]. Major surgery reduces 40% of physiological reserve. Four weeks after discharge patients report pain, physical fatigue, reduced appetite, trouble sleeping, reduced ability to concentrate [96]. Functional capacity may not be fully recovered up to 6–9 weeks [97] and so for the elderly patients, at 8 weeks, at most one third and at 6 months after surgery only 50% recover to preoperative levels [95, 98].

Due to the increasing age of patients undergoing major abdominal surgery there is a subsequent increase in postoperative complications, prolonged hospital stays, mortality rates and also health care costs. "Frail" elderly patients frequently develop delirium as a sever complication. The primary study outcome of one single-center controlled before-and-after study, in progress, is to reduce the incidence of delirium in elderly patients regarding of major abdominal surgery applying principles of multicomponent prehabilitation pathway [99].

There is emerging evidence suggesting that many of the negative effects of major surgery can be reduced through the attenuation of surgical stress, not only due to intraoperative (minimally invasive surgery [99], fluid management [100], etc.), or postoperative (e.g., "fast track" early nutrition, mobilization [101]) interventions but also with the effort to focus on the preoperative period and accelerate convalescence [21].

Despite this evidence, surgical prehabilitation is not yet a component of routine clinical practice. Prehabilitation as a multicomponent approach requires an interdisciplinary cooperation, as it offers a shift from the current healthcare paradigm, just as PPPM/3 PM represents a paradigm change, and these two changes are well in agreement. Preoperative period proposes the best opportunity for preventive targeted (personalized) interventions in order to improve more effective healthcare and postoperative recovery [12].

Preoperative prehabilitation involve four main pillars and goals—nutritional optimization (recognition of malnourished patients, identification deficiencies in patient's eating, provision of holistic nutritional management including nutritional supplementation, etc.), exercise and physical activity (individualized exercise program, combining aerobic, and intensity training) and psychological well-being (anxiety and stress reducing techniques, interventions to improve cognitive function) [12]. As a part of prehabilition patients should be profusely support to cease smoking [85]. Additionally to these elements of multimodal approach, we suggest that prehabilitation, from the perspective of PPPM/3 PM, should also include other elements as already highlighted in Fig. 1.

2.8 Peri-Operative, Intraoperative Prehabilitation and PPPM/3 PM

The optional surgery pathways provide the caregiver an opportunity for significant changes in the attitude the care is arranged—instead of taking provider convenience into fundamental consideration the patient needs are primarily considered. Redesigning peri-operative pathways helps to improve the provided care for the patient and increase the quality of services, patient's satisfaction, public health as well as healthcare value, defined as outcome per unit of currency [102]. Episodic peri-operative care in some systems accounts for over half of hospital costs [103].

Multidisciplinary medical care of patient from the intention of undergoing surgery until full recovery is defined as peri-operative medicine [104, 105]. Peri-operative medicine is a new and rapidly evolving clinical science that is well in agreement with the attitude of PPPM, and respond to the needs of a population of patients with more complex medical management. Peri-operative medicine means the ability to prepare patients beyond the traditional anesthetic and surgical care of a single patient (personalization) in the early, preventive peri-operative period [106]. Elective peri-operative care helps to rationalize and redesign more advantageous patients care. Providing patients care with the possibility of predicting the risk of adverse outcome, the so-called risk-adapted approach, improve the value of healthcare delivery [102].

The goal is patient-centered care of their own, their wishes, expectations, opinions, on the other hand management around surgical procedure resulting in their best interest, adequate preparation for the surgery and enhanced recovery after surgery [102].

Avoiding "wrong-patient surgery," serving patient's best interests with improved patient-physician experience, together with effective management of comorbidities with the intention of mitigating the risk of major surgery, cooperation with pain clinics, that and lot more at the same time offer the preoperative period [107].

During the preoperative period, patients may be more susceptible to behavior change interventions. Smoking cessation, alcohol cessation, nutritional optimization and physical activity and exercise. Such changes in behavior at a time when patients may feel very limited control of their immediate destiny may have significant psychological benefit and may be long-lasting which also highlights possible population health benefits.

Regarding intra-operative care the published data support the idea that numerous factors provided for the patients do not follow provable evidence and/or a comprehensive medical basis which results in the situation when particular factors are not essentially those which one might expect in everyday life. Even if we may consider alternatives for these factors resulting from the patient and surgery-specific characteristics (e.g., age, risk factors, duration of surgery, amount of blood loss), the most significant effect would have anesthesia and providers of surgery. (e.g., fluid therapy) [108]. On the basis of related studies and examinations we support the opinion that intra-operative care must essentially be standardized to provide particular standard level of quality and patterns of care for

wide spectrum of patients, as well as it must be personalized/individualized in order to include patient-specific characteristics which might be unique and important for good result [102].

2.9 Management of Comorbidities as Important Element of Prehabilitation

The growing prevalence of comorbid conditions [103], and harmful lifestyle characteristics (e.g., inactivity, unbalanced diet, stress, intoxication from environment and other resources, cigarette smoking, alcohol abuse, etc.) coupled with an understanding that some surgery may be unnecessary or even harmful [109] are driving a re-appraisal of peri-operative processes. Patients who are candidates for surgery are often not ready for it [102].

Risk of problems after surgery, or a medical procedure in general, is the product of particular probability(ies) consequently leading to undesirable outcome(s). The probability of a particular peri-operative episode is determined by both, patient characteristics and healthcare characteristics (taking into consideration all aspects of peri-operative care and surgery itself). Together, these risk determinants can be preventively reduced by implementation of particular changes in peri-operative procedures. We distinguish between permanent risk factors and modifiable risk factors which may be adjusted or changed ahead of the scheduled time of the surgery or a medical procedure. There are, of course, several factors such as age, sex or genetic predispositions which can't be changed. Other factors, on the other hand, have the potential for modification or for being influenced; for example, emphysema, myocardial injury, anemia, reversible airway disease can be partly resolved. Among risk factors that can be substantially modified, if the patient is properly motivated and well instructed, there are factors such as consumption of alcohol and tobacco, drugs, low physical activity, unbalanced diet, psychological stress—all related to life style and behavior [102] and are well in agreement with the attitude of PPPM/3 PM.

2.10 Postoperative Procedures, DrEaMing, in Relation to Prehabilitation and PPPM/3 PM

Patients with an uncomplicated recovery should be discharged and return to normal life as quickly as possible. Higher-risk patients or patients developing postoperative complications should be provided with the appropriate level of care without delay and on a predictive, preventive, and personalized basis where possible.

Providing care based on effectiveness of use, not traditionally used procedures, more patient-oriented postoperative care, the flexible use of health professional resources to maximize effectiveness and minimizing risks through more effective communication and systematized actions like checklists, risk-adapted management of postoperative period, all this can increase and underpin efficiency of postoperative care.

Patients who achieve Drinking Eating and Mobilizing (DrEaMing) [110] rarely develop postoperative complications, so concept of DrEaMing is solid marker of recovery and benchmark of the effectiveness of peri-operative care [110].

2.11 Conclusion and Recommendations

In conclusion, the idea of prehabilitation and its practical application is enriching the vision of PPPM/3 PM in a very natural and logical way. Although the prehabilitation is being primarily connected to the surgical procedures, it should be, in our opinion, applied to much wider spectrum of personalized medical procedures that would include: surgery, stomatosurgery, plastic surgery, childbirth, application of physiotherapy, pharmacotherapy, radiotherapy, chemotherapy, traditional, complementary and alternative medicine (TCAM), invasive diagnostic procedures, and other.

We suggest that basic elements of prehabilitation should include also other factors and tools as visualized in the complex prehabilitation in Fig. 1. The communities of experts in surgery, oncology, prehabilitation, peri-operative care and postoperative care may benefit from the tools developed under PPPM/3MP and vice versa, the attitudes in the prehabilitation fit very well within PPPM/3 PM and represent a very good example of practical implementation of PPPM from bench to bedside. The conscious cooperation between the experts in all related fields will essentially bring benefits to all patients and gradually prepare the ground for effective future healthcare.

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