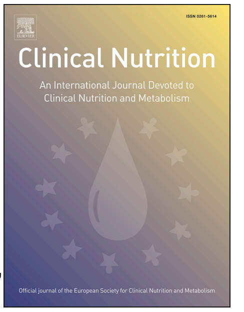

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Abstract

Background and aims: Malnutrition has been recognized as a major risk factor for adverse postoperative outcomes. The ESPEN Symposium on perioperative nutrition was held in Nottingham, UK, on 14-15 October 2018 and the aims of this document were to highlight the scientific basis for the nutritional and metabolic management of surgical patients.

Methods: This paper represents the opinion of experts in this multidisciplinary field and those of a patient and caregiver, based on current evidence. It highlights the current state of the art.

Results: Surgical patients may present with varying degrees of malnutrition, sarcopenia, cachexia, obesity and myosteatosis. Preoperative optimization can help improve outcomes. Perioperative fluid therapy should aim at keeping the patient in as near zero fluid and electrolyte balance as possible. Similarly, glycemic control is especially important in those patients with poorly controlled diabetes, with a stepwise increase in the risk of infectious complications and mortality per increasing HbA1c. Immobilization can induce a decline in basal energy expenditure, reduced insulin sensitivity, anabolic resistance to protein nutrition and muscle strength, all of which impair clinical outcomes. There is a role for pharmaconutrition, pre-, pro- and syn- biotics, with the evidence being stronger in those undergoing surgery for gastrointestinal cancer.

Conclusions: Nutritional assessment of the surgical patient together with the appropriate interventions to restore the energy deficit, avoid weight loss, preserve the gut microbiome and improve functional performance are all necessary components of the nutritional, metabolic and functional conditioning of the surgical patient.

1. Introduction

Major surgery evokes a catabolic response that results in inflammation, protein catabolism and nitrogen losses. This response is proportional to the magnitude of the procedure and can, in some instances, be detrimental to the patient, especially when there is pre-existing malnutrition. Traditional perioperative care has involved measures that starve the patient for prolonged periods of time, stress the patient with measures that amplify this response and drown the patient with salt and water overload. However, over the past two decades, there has been a paradigm shift in perioperative care, with periods of starvation being reduced drastically, introduction of measures to reduce surgical stress and protein catabolism, and avoiding salt and water overload. The aim of modern perioperative care is to attenuate loss of or aid return to function in an accelerated manner by promoting return of gastrointestinal function, feeding the patient early, providing adequate pain relief, and encouraging early mobilization. These measures result in reduced complications, early discharge from hospital without increasing readmission rates and better functional recovery.

The European Society for Clinical Nutrition and Metabolism (ESPEN) has published updated evidence-based guidelines on perioperative nutrition recently that help aid the nutritional care of the surgical patient [1]. In further support of these guidelines, an ESPEN expert group met for a Perioperative Nutrition Symposium in Nottingham, UK on October 14 and 15, 2018. The group examined the causes and consequences of preoperative malnutrition, reviewed currently available treatment approaches in the pre- and postoperative periods, and analyzed the rationale on which clinicians could take actions that facilitate optimal nutritional and metabolic care in perioperative practice. The content of this position paper is based on presentations and discussions at the Nottingham meeting along with a subsequent update of the literature.

2. Historical note

Our understanding of the concept of clinical nutrition and the science of human nutrition has evolved significantly over the last two decades. The role of nutrition in surgery has encompassed measures to recognize, identify and intervene in those pre-operative patients who are at risk of malnutrition with appreciable impact on post-surgical outcomes in those adequately nutritionally prehabilitated. However, it would be incorrect to consider clinical nutrition as an entirely new concept [2-4]. Ancient Egyptians were the first to be credited with descriptions befitting enteral nutritional as identified in the Ebers papyrus (c 1550 BC) [4] and feeding via the oropharyngeal and nasopharyngeal routes are from then on described throughout the antiquated medical literature. For instance, Capivacceus in the 16th century, Aquapendente in the 17th century [2, 4] and the 19th century physician Dukes [5] employed these routes of nutritional delivery to treat all manner of ailments including mania, diphtheria and croup.

The recognition of nutritional deficiency as a cause of illness was first presented by James Lind, a fellow of the Royal College of Physicians of Edinburgh who established the superiority of citrus fruits above all other 'remedies' in his treatise on scurvy published in

1753 [6]. The identification, characterization and synthesis of essential vitamins and minerals during the earlier part of the 20th century [7], allowing their use in the treatment of nutritional deficiency-related diseases such as scurvy, pellagra, rickets, and nutritional anemias [7].

The adverse effect of weight loss on surgical outcome was documented over 80 years ago when Hiram Studley showed that, in patients undergoing surgery for perforated duodenal ulcer, postoperative mortality was 10 times greater in those who had lost more than 20% of their body weight preoperatively when compared with those who had lost less [8]. This observation generated much of the ensuing work to define the role of malnutrition, nutritional deficiencies, and perioperative nutrition in surgery.

3. The malnourished surgical patient

The definition of a malnourished patient is the subject of ongoing discussion. In the last decade there have been considerable efforts to rationalize various definitions generally, and in the cancer patient for whom surgery is commonly the primary modality for cure. The starting point for much of this work was the international consensus of 2011 [9]. In this publication, cancer cachexia was defined as “a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.” There was a recognition of the role of the systemic inflammatory response in the symptoms associated with cachexia. Serum CRP was agreed to be an important biomarker, but it was recognized that cachexia can be present in the absence of overt systemic inflammation [10].

In the intervening years with greater knowledge of the importance of systemic inflammatory responses in the progressive nutritional and functional decline of patients with cancer, this statement has been increasingly called into question and measurement of the magnitude of the systemic inflammatory is now integral to the definition and treatment of cancer cachexia [11-14]. This more nuanced definition reflects the evolution of criteria in the definition of malnutrition in which cancer cachexia is considered as part of disease related malnutrition with inflammation [15, 16]. For example, approximately 40% of patients with operable colorectal cancer considered at medium or high nutritional risk (malnutrition universal screening tool – MUST [17]) had evidence of systemic inflammation (CRP>10 mg/L) [18].

4. Sarcopenia, sarcopenic obesity and myosteatosis

Patients may present to surgery with a range of underlying nutritional syndromes and phenotypes, such as malnutrition, sarcopenia, cachexia, obesity and myosteatosis. Furthermore, these phenotypes are associated with worsened post-operative outcome. However, screening for such syndromes is not necessarily performed routinely in clinical practice, and there is no one screening tool that is capable of distinguishing one syndrome from another [19].

4.1 Sarcopenia

A recent study showed that the surgical population in the UK tends to be older than the general population, and that the age gap is increasing with time. Between 1999 and 2015, the percentage of people aged 75 years or more undergoing surgery increased from 14.9% to 22·9%, and this figure is expected to increase further [20]. Sarcopenia is described as 'the loss of skeletal muscle mass and strength as a result of ageing'. There are a number of definitions for sarcopenia, which rely on the measurement of the combination of both muscle function and muscle mass. These include the European Working Group of Sarcopenia in Older Persons (EWGSOP) [21], the International Working Group on Sarcopenia (IWGS) Sarcopenia Task Force [22], the Asian Working Group for Sarcopenia and the Foundation for the National Institutes for Health (**Table 1**) [10, 21-25].

More recently, the term "sarcopenia" has taken on a different usage. The use of diagnostic cross-sectional computed tomography (CT) images at the third lumbar vertebral level (L3) for the simultaneous perioperative analysis of body composition has become increasingly popular [26]. In this surgical context, sarcopenia has come to mean reduced muscularity, without assessment of patient functional status. Rather than assessing skeletal muscle mass, this CT technique analyses cross-sectional skeletal muscle area which is then indexed to patient height to give a skeletal muscle volume. This technique also provides data on the mean skeletal muscle radiodensity, quoted in Hounsfield Units (HU), which is a surrogate marker of muscle quality and an indication of the presence of myosteatosis, as well as adiposity in terms of both visceral and subcutaneous fat cross-sectional area and indices. There is a large volume of literature linking preoperative sarcopenia in a range of different pathologies, including pancreatic surgery [27], gastric cancer surgery [28], esophageal cancer [29], liver transplantation [30] and colorectal cancer [31] to worsened clinical outcomes and overall survival. The strength of this relationship is even greater when the presence of sarcopenia is combined with obesity, i.e. low muscle volume in association with elevated body adiposity. A recent meta-analysis has examined this relationship in 2297 patients with pancreatic ductal adenocarcinoma, finding both sarcopenia and sarcopenic obesity to be associated with poorer overall survival (HR 1.49, $p<0.001$ and HR 2.01, $p<0.001$) [32].

However, there are problems of interpretation in the literature, often due to heterogeneity in the methodology of the studies leading to variability in results. There has been a degree of variability in the cut-offs used for the diagnosis of sarcopenia (and myosteatosis). However, there are well validated BMI and gender-specific cut-offs available in the literature for cancer patients [33]. The validated technique uses CT-based analysis at the L3 level, as this was the level that the initial validation calculations were performed in order to extrapolate to the whole body. Recently, several studies have looked at body composition analysis at the fourth thoracic vertebra as an alternative in patients who are undergoing a thoracic rather than abdominal procedure [34].

4.2 Myosteatosis

Myosteatosis is the infiltration of skeletal muscle by fat, into both intermuscular and intramuscular compartments. There are a multitude of different terms used synonymously with myosteatosis, including muscle quality, radiodensity, and muscle attenuation. There has been significant research interest in the impact of myosteatosis on surgical outcomes in a range of different cancer types, including periampullary [35], ovarian [36] and rectal cancer [37]. As with the relationship between sarcopenia and obesity, there also appears to be a combined effect with myosteatosis and obesity. In a series of 2100 patients undergoing elective colorectal cancer surgery, three body composition subtypes were independent predictors of hospital length of stay; combined sarcopenia and myosteatosis (incidence rate ratio (IRR) 1.25,), visceral obesity (IRR 1.25,) and myosteatosis combined with sarcopenia and visceral obesity (IRR 1.58). The risk of readmission was associated with visceral obesity alone (OR 2.66, p=0.018), visceral obesity combined with myosteatosis (OR 2.72, p=0.005) and visceral obesity combined with both myosteatosis and sarcopenia (OR 2.98, p=0.038). There is also emerging evidence that low skeletal muscle radiodensity is involved in the etiology of, or shares mechanisms with, other comorbidities such as myocardial infarction, diabetes and renal failure [38].

4.3 Cachexia

The third body composition syndrome of interest is cachexia, which occurs as a consequence of a range of diseases, including cancer, chronic obstructive pulmonary disease, cardiac failure, renal failure and rheumatoid arthritis. Cachexia is multifactorial in etiology [39]. For example, in patients with cancer, not only is the tumor a potential driver for nutritional depletion, but patients also tend to be older (hence, sarcopenic), live a sedentary lifestyle, and often have a poor diet, as well as have other comorbidities which may impact upon body composition. Recent evidence also suggests that some cancer patients may have a genetic predisposition to weight loss and low muscularity [40].

There have been a number of definitions of cachexia published previously [25, 41-43]. However, the most accepted definition of cancer cachexia is ‘’a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment’ [10]. This international consensus provided diagnostic criterial which were either weight loss exceeding 5% or weight loss greater than 2% in individuals already showing depletion as marked by a BMI <20 kg/m^2 or the presence of sarcopenia.

The interaction and overlap between sarcopenia, myosteatosis and cancer cachexia are not currently well understood. In addition, the interaction between these skeletal muscle variants and patient adiposity and frailty are not clear and these should be the focus of research in the future.

5. The metabolic response to immobilization and surgical trauma

There are a number of different factors which contribute to the peri- and post-surgical trauma phenotype including immobilization, reduced oral intake, anesthesia, tissue damage, subsequent immune system activation and metabolic changes.

There are significant metabolic changes associated with a period of bedrest which are paralleled in the metabolic changes occurring after surgery [44] as immobilization is one of the key components of postoperative changes. These negative changes are also observed in clinical populations and sarcopenic or frail older adults [45] and include a decline in basal energy expenditure, reduced insulin sensitivity, anabolic resistance to protein nutrition, muscle strength and physical performance as well as increased risk of falls, health-related expenditure, morbidity and mortality. The larger impact of bed rest on the rate of loss of lean muscle leg mass and strength during bedrest in healthy older adults than their young counterparts is equivocal [46, 47]. On the other hand, gain of muscle mass and function as a consequence of exercise requires significant regular training over an extended period of time, with evidence suggesting that 12 weeks of resistance exercise training is necessary for a 1.5 kg gain in muscle mass in older adults [45].

As the process of muscle loss requires a considerably shorter period of time in older adults, with just seven days of bedrest resulting in 1 kg loss of lean leg muscle mass, there should, therefore, be a particular emphasis on the preservation of muscle mass during periods of muscle disuse whilst older patients are in hospital. This loss of muscle mass occurs in both the type I (slow twitch) and type II (fast twitch) skeletal muscle fibers [48]. In terms of muscle strength, the initial loss of strength occurs rapidly during a period of immobilization, irrespective of the cause of immobilization. However, this loss of strength then plateaus after around 30 days.

Older adults tend to stay longer in hospitals and after discharge experience a more pronounced decrease in ambulatory function and reduced ability to complete activities of daily living. There are a number of strategies which have been recommended to reduce muscle wasting during bedrest in older adults, including resistance exercise [49], dietary interventions such as an increase in protein intake to exceed 1 g/kg body weight/day, administration of essential amino acid (EAA) mixtures [50, 51], as well as the combination of these EAA mixtures with carbohydrate [52] or leucine, valine and isoleucine. A study [51] on the role of essential amino acids in older adults undergoing 10 days best rest found that although this normalized muscle protein synthesis, it did not have an effect upon skeletal muscle loss or function. However, when beta-hydroxy-beta-methylbutyrate (HMB) supplementation was used in a randomized placebo-controlled trial [46] in healthy volunteers undergoing a period of 10 days bedrest, this resulted in a significant reduction in the amount of muscle loss associated with the bedrest as well as an increase in muscle mass gain during the 8 week rehabilitation phase, both in terms of total lean mass and total leg lean mass. Muscle strength also appeared to be preserved in this study.

There are many parallels to that associated with immobilization when bedrest as a consequence of surgery is considered. Preoperative fasting is associated with characteristic metabolic changes. After just a short overnight fast, the body remains able to cope with the glucose demands placed on it by the muscle, brain, kidney, bone marrow and lymph nodes by the breakdown or glycogen within the liver. However, after starvation of 24 hours, the metabolic response changes to the breakdown of adipose tissue to mobilize fatty acids which are utilized by the muscle and kidney. When more prolonged periods of fasting are considered, the metabolic response become somewhat more complex. Muscle protein breakdown releases amino acids such as alanine and glutamine which are used in the kidney and liver to promote gluconeogenesis, with persistence of adipose tissue breakdown to provide ongoing energy stores.

Resting energy expenditure (REE) increases after surgery, with the degree determined by the magnitude of the insult, with most pronounced changes observed in those following major burns, followed by those with sepsis or peritonitis. Elective surgery is associated with a much lower increase in REE. The metabolic response to surgical trauma allows mobilization of glucose and glutamine to provide substrate for wound healing, and amino acids for acute phase protein synthesis. Intensive care unit stay is also associated with a typical pattern of skeletal muscle loss [53] which is far more rapid than that seen after a standard surgical insult.

Surgery results in an overall reduction in lean leg muscle mass [54]. However, when protein turnover is examined, there is not a large difference between the pre- and post-operative phases. When patients are fed postoperatively, this results in a significant increase in protein synthesis rates and reduction in protein breakdown when compared with patients who were fasted postoperatively [54]. Changes in skeletal muscle mass and function following surgery are most likely the consequence of inactivity combined with reduced food intake and specific metabolic changes.

6. Nutrition and surgical outcome – lessons from the ESPEN nutritionDay

In the nutritionDay dataset [55] (155 524 patients) 41% of the enrolled participants were surgical patients. The median length of stay for the cross-sectional nutritionDay data collection was 6 days for surgical and non-surgical patients [56]. Surgical patients were 6 years younger than non-surgical patients (63 *vs*. 69 years, p<0.001). BMI was similar in surgical and non-surgical patients. BMI was <18.5 kg/m^2 in 7.1% of patients and was >30 kg/m^2 in 19%.

Weight loss within the last 3 months was slightly less frequent in surgical patients (39%) than in non-surgical patients (43%) (p<0.0001) while stable weight was more frequent in surgical patients (40% *vs*. 33%, p<0.0001). Reduced intake in the week before nutritionDay" was slightly less frequent in surgical (44%) than in non-surgical (46%) patients (p<0.0001). On nutritionDay the full served meal was eaten by only 35% of surgical patients vs 38% of non-surgical patients. Nothing was eaten by 20% of surgical patients and 11% of non-surgical patients mostly because they were not allowed to eat. The high proportion of surgical patients with nothing eaten on nutritionDay is shown in **Figure 1** for preoperative, postoperative and non-surgical patients. Artificial nutrition was used in a minority of patients eating nothing. In patients not allowed to eat 30% received artificial nutrition, and in patients eating nothing despite being allowed to eat 27% received artificial nutrition. Reduced eating was associated with a delay in discharge of about 1 day. Outcome at day 30 after nutritionDay was available for 83% of patients. Most patients (72.5%) were discharged home 3.8% had died in hospital. Mortality was lower in surgical patients (2%) when compared with non-surgical patients (5%).

Weight loss was associated with a slightly higher odds ratio for death in hospital within 30 days in surgical patients when compared with non-surgical patients (OR 3.2 vs 2.5). Reduced intake in the previous week was associated with a progressive increase in death within 30 days from OR 2.0 for less than normal eating, OR 3.6 for eating half and OR 6.4 for eating less than a quarter. This association was similar at all levels to non-surgical patients. Eating half the recommended amount in hospital on nutritionDay was associated with an OR 2.3 of death whereas eating nothing despite being allowed to eat was associated with an OR 9.0 (**Figure 1**).

7. The patient at risk and nutritional assessment

The German hospital malnutrition study [57] found that overall 27.4% of patients were diagnosed with malnutrition according to the subjective global assessment (SGA), with a huge degree of variability between specialties. In patients who had undergone major abdominal surgery the prevalence of malnutrition was 44%, with lowest rates in those undergoing chest or general surgery (20% and 14%, respectively). A study of 26 hospital departments spread across the European Union using the nutritional risk screening (NRS-2002) tool identified that 32.6% of patients were at 'high risk' of malnutrition, with these patients developing more complications (30.6% vs 11.3% $p<0.001$) , increased mortality rates (12% vs. 1%, $p<0.001$) and longer hospital length of stay (median 9 vs. 6 days, $p<0.001$) when compared with patients who were 'not-at-risk'. A progressive degree of malnutrition, from none to severe, has been associated with progressive increased risk of morbidity and mortality as well as increased ICU admission and overall hospital length of stay in patients undergoing liver transplantation [58]. This relationship of increased morbidity and mortality amongst those with malnutrition is also seen in those undergoing abdominal surgery for cancer [59].

Many of the screening tools used historically to identify those at high risk of malnutrition considered only single parameters. However, these do not facilitate the identification of patients' preoperative nutritional status, nor do they precisely identify those at high nutritional risk [60]. A validated screening tool offers a far superior method for identifying those at high risk of malnutrition correctly. Four central criteria were proposed to identify those at high nutritional risk; body mass index (BMI) and a detailed nutritional history, the presence of pathological weight loss, appetite and food intake and the severity of the underlying disease. This led to the development of a range of screening tools including the malnutrition screening tool (MST), the malnutrition universal screening tool (MUST) [17], the nutrition risk index (NRI) [61], the subjective global assessment (SGA) [62], the mini nutritional assessment short form (MNA-SF) [63] and the nutritional risk screening (NRS-2002) [64]. There is only expert consensus regarding the best screening tool available for nutritional risk assessment, which suggests that the MUST is superior in the community, NRS 2002 for inpatients and SF-MNA for those in older adult care homes. A multitude of studies have subsequently been performed to validate the predictive value for complications and mortality of preoperative NRS 2002 in patients undergoing surgery, including gastric cancer surgery [65], colorectal surgery [66] and major gastrointestinal surgery [67, 68]. A meta-analysis [69] examining the use of NRS 2002 as a predictor of postoperative outcomes in abdominal surgery included a total of 11 studies. Postoperative complications were more frequent in those deemed 'at risk' than those 'not-at-risk' (OR 3.13, p<0.00001). Mortality was also higher in patients 'at risk' (OR 3.61, p=0.009) and these patients had a significantly longer hospital LOS (mean difference 3.99 days, p=0.01) [69].

More recent guidelines [1] have explored criteria for the diagnosis of severe nutritional risk, and these have included weight loss exceeding 10-15% within the preceding 6 months, BMI less than 18.5 kg/m^2, NRS 2002 >5 or SGA grade C or a preoperative serum albumin concentration less than 30 g/L in the absence of hepatic or renal dysfunction. If one of these criteria is present, targeted nutritional therapy should be instigated immediately. If the screening tools discussed previously identify a patient at risk, a more formal and extensive nutritional assessment should be performed by an appropriately trained professional. This assessment should include nutritional assessment using a plate chart or 24-hour dietary recall, estimation of patients subcutaneous and visceral adiposity and skeletal muscle mass, other anthropometrics measures such as upper arm circumference and skin-fold thickness; hand-grip strength as a test of muscle function; and Barthel index or 6-minute walking test as a measure of body function [70].

8. Preoperative nutritional and metabolic preparation of the surgical patient

Preoperative conditioning is defined as the process of training to become physically fit by a regimen of exercise, diet and rest and is, therefore, regarded as a multimodal intervention. Perioperative oral nutrition is considered one of the major preoperative components of Enhanced Recovery After Surgery (ERAS) pathways [71]. ERAS is believed to help by 'exploiting the critical perioperative period to improve long-term cancer outcomes' [72], and optimization of nutrition is one area which can be exploited successfully.

The concept of preoperative conditioning is not a new one. In 1992 the concept of a 'decision box' [73] which helps to identify the right patients who will benefit most from a nutritional intervention, was devised. Given the high prevalence of malnutrition discussed in the previous section and the known risk factors, which are highly prevalent amongst those undergoing surgery, this should be aggressively targeted. The metabolic risk is exacerbated in patients with malignancy [74] due to release of TNF-alpha, IL-6 and IL-1 in addition to anorexia caused by central nervous system signaling which results in muscle wasting, changes in liver metabolism as well as consumption and depletion of fat stores. Exercise is one modality which can help modulate these metabolic consequences of tumor, by promoting IGF-1, mTOR, and Akt which results in increased protein synthesis; IL-10, sTNF-r1 and sTNF-r2 which reduces systemic inflammation; GLUT-4 which reduces insulin resistance and SOD and GSH which results in a reduction in the formation of reactive oxygen species [75].

The aims of preoperative conditioning are to restore the energy deficit, improve functional performance, avoid weight loss and preserve the gut microbiome. To obtain such effect, a normocaloric diet is sufficient with a protein intake of 1.2 g/kg [76]. The intervention should include dietary counselling, fortified diets, oral nutritional supplementation (ONS), and parenteral support, where indicated. The enteral route is always preferred wherever feasible and even when patients are consuming a normal diet this is frequently insufficient to obtain their energy requirement, so it is recommended that patients receive oral nutritional supplements (ONS) in the preoperative period, irrespective of their nutritional status [1]. There is good evidence to support ONS in the perioperative period, with a meta-analysis of 9 studies [77] finding this to be associated with a 35% reduction in total complications ($p<0.001$) and this translated to a cost saving and to be cost effective. In those patients who are identified as high-risk undergoing major abdominal surgery and those who are malnourished with a diagnosis of cancer, ONS should be considered obligatory [1]. In terms of parenteral nutrition (PN), this should only be considered in those with malnutrition or severe nutritional risk where emergency requirements cannot be met by enteral nutrition interventions alone [1]. Where this approach is absolutely necessary, PN should be provided for 7-14 days preoperatively to maximize benefit, based upon evidence that this time frame is necessary to reduce the Clavien-Dindo grade 3b or higher surgical site infection-based complications [78].

The use of carbohydrate loading as metabolic conditioning is supported by some basic science and clinical studies [79, 80]. A recent large prospective randomized clinical trial has shown significant benefits regarding the reduction of postoperative insulin resistance and hyperglycemia without impact on the complication rate [81]. So far, the evidence for a decrease of postoperative morbidity is not yet clear.

Prehabilitation has gained popularity in recent times, with increasing evidence to support a multimodal prehabilitation program in a range of surgical specialties. A study combining a 6-week preoperative bundle of physical exercise and endurance training, nutrition interventions and psychological support to improve anxiety when compared to postoperative rehabilitation alone [82] in a cohort of patients undergoing elective colorectal surgery found that this optimizes the patients functional capacity throughout the perioperative period. In those patients who are due to undergo preoperative neoadjuvant therapy, the period after cessation of therapy but prior to surgery is typically 4 to 6 weeks and this time should be exploited to optimize patient fitness. A meta-analysis of multimodal prehabilitation [83] in elective colorectal surgery found that this was associated with a significant reduction in hospital LOS of 2 days and was linked to a faster time to return to presurgical functional capacity. When pooled data from RCTs regarding trimodal prehabilitation was analyzed [84], this found that the postoperative loss of lean body mass was attenuated in patients undergoing prehabilitation versus rehabilitation alone. There is also support that a multimodal intervention is associated with improved perioperative physiological parameters, functional outcomes and quality of life measures, but no impact on postoperative complications in those undergoing liver resection [85] as well as a beneficial effect in muscle strength in sarcopenic older adult patients undergoing gastric cancer resection [86]. In high-risk patients undergoing elective major abdominal surgery, a randomized controlled trial found that prehabilitation in the form of a motivational interview, high-intensity endurance training and promotion of physical activity was associated with a significant reduction in the incidence of postoperative complication [87] (31% vs. 62%, p=0.001).

9. Perioperative glycemic control

Hospital guidelines surrounding perioperative glycemic control are based, in 90% of cases, on the guidance published by Diabetes UK in 2011 [88]. This provides a standard of care, which should be met commencing at the point of referral from primary care, through the perioperative stage and to discharge from hospital. At the first stage when the patient is referred from primary care, the minimum information that should be provided should include the duration and type of diabetes, the place of usual diabetes care (primary or secondary), other comorbidities, and treatment (both for the diabetes and other comorbidities). Information should also be provided on details of any diabetes-associated complications such as renal or cardiac disease, and finally any relevant measures from within the last 3 months, including body mass index (BMI), blood pressure, HbA1c and eGFR. However, the compliance to this standard was low [89].

There is evidence supporting an association between the presence of diabetes and significantly elevated risk of 30-day mortality in patients undergoing elective non-cardiac surgery [90]. Those patients with diabetes (20.2%) with preoperative hyperglycemia (7.9%) were twice as likely to die as those with a normal preoperative glucose concentration. However, if the patient did not have preoperatively diagnosed diabetes but had preoperative hyperglycemia, they were 13 times more likely to die within 30 days of surgery when compared with a patient with normal preoperative glucose concentration. When postoperative hyperglycemia was considered, if the patient were not diagnosed with diabetes but had perioperative or postoperative hyperglycemia, they were 45 times more likely to die than those with normal glucose concentration. There is also an association between hyperglycemia in those who were previously normoglycemic and composite adverse events [91], as well as reoperative interventions, anastomotic failures, myocardial infarction and composite infections [92]. However, knowing that the patient was diabetic in the presence of hyperglycemia attenuated these worse clinical outcomes by almost half. There is consistent evidence that the highest risk group with regards to perioperative glucose control are those who are not diagnosed with diabetes but who develop postoperative hyperglycemia.

Clinical outcomes in those with poorly controlled diabetes are significantly worse than those with well-controlled diabetes, with a stepwise increase in the risk of infectious complications and mortality relating to infection according to increasing HbA1c (RR 0.98, if HbA1c <6% versus RR 2.01, if HbA1c ≥11%) [93]. Patients with highest preoperative HbA1c levels tend to have their blood glucose levels checked earlier, have higher postoperative glucose concentrations and are significantly more likely to be commenced on insulin postoperatively, than those with a lower preoperative HbA1c, possibly due to an elevated level of vigilance [94].

The current National Institute for Health and Care Excellence (NICE) clinical guideline 45 surrounding the use of routine preoperative tests prior to elective surgery suggests that HbA1c should only be routinely tested in those patients with a formal diagnosis of diabetes [95]. However, this is a controversial policy as it fails to identify those patients with non-diabetic hyperglycemia [96] and, therefore, misses the opportunity to intervene preoperatively and modify the elevated perioperative surgical risk that this is associated with.

10 Perioperative fluids and outcome

There is a close relationship between nutrition and fluid and electrolyte balance, with the intake of food by natural or artificial means being inseparable from that of fluid and electrolytes [97]. The metabolic response to surgery is associated with salt and water retention and an increase in the excretion of potassium, as a result of which patients are susceptible to retention of salt and water, and consequent fluid overload in the perioperative period [98-103]. There is a relatively narrow margin of safety in perioperative fluid therapy and either too much or too little can have a negative effect on physiological processes and clinical outcome. The goal of perioperative intravenous fluid therapy should be to maintain tissue perfusion and cellular oxygen delivery, while at the same time keeping the patient in as near zero fluid and electrolyte balance as possible (**Figure 2**).

10.1 Preoperative period

Patients should reach the anesthesia room in a state as close to euvolemia as possible with any preoperative fluid and electrolyte imbalance having been corrected. Current anaesthetic recommendations that allow patients to eat for up to 6 h and drink clear fluids up to 2 h prior to the induction of anesthesia help to prevent preoperative fluid depletion without increasing aspiration-related complications. Some patients may need intravenous fluids to restore euvolemia prior to surgery.

10.2 Intraoperative period

Most patients require crystalloids at a rate of 1-4 ml/kg/h to maintain homeostasis [104]. However, some patients develop intravascular volume deficits which require correction by administration of goal-directed boluses of intravenous solutions. Goal directed fluid therapy (GDFT) is aimed at maintaining intravascular normovolemia guided by changes in stroke volume as measured by a minimally invasive cardiac output monitor to optimize the position of each patient on his/her individual Frank–Starling curve [105, 106]. In addition to the background crystalloid infusion, fluid boluses (200-250 ml) should be given to treat any objective evidence of hypovolaemia (>10% fall in stroke volume) in order to optimise intravascular volume and cardiac output [107]. A recent meta-analysis that included 23 studies with 2099 patients has shown that GDFT was associated with a significant reduction in morbidity, hospital length of stay, intensive care length of stay, and time to passage of feces [108]. However, when patients were managed within ERAS pathways, with optimal perioperative care and avoidance of postoperative fluid overload, the only significant reductions were in length of intensive care stay and time to passage of feces. It has also been shown that GDFT does not impact on outcome when compared with conventional intraoperative fluid therapy in patients undergoing elective colorectal surgery [109]. Hence, within ERAS programmes, it may not be necessary to offer all patients GDFT, which should be reserved for high risk patients or for patients undergoing high risk procedures [104].

10.3 Postoperative period

For most patients undergoing elective surgery, intravenous fluid therapy is usually unnecessary beyond the day of operation, except for those undergoing upper gastrointestinal and pancreatic procedures. With these exceptions, patients should be encouraged to drink as soon as they are awake and free of nausea after the operation. An oral diet can usually be started on the morning after surgery [110, 111]. When adequate oral fluid intake is tolerated, intravenous fluid administration should be discontinued and be restarted only if required to maintain fluid and electrolyte balance. If intravenous fluids are required, then in the absence of ongoing losses, only maintenance fluids should be given at a rate of 25-30 ml/kg/day with no more than 70-100 mmol sodium/day, along with potassium supplements (up to 1 mmol/kg/day) [112]. As long as this volume is not exceeded, hyponatraemia is very unlikely to occur despite the provision of hypotonic solutions [113, 114]. Any ongoing losses (e.g. vomiting or high stoma losses) should be replaced on a like-for-like basis, in addition to maintenance requirements. After ensuring the patient is normovolemic, hypotensive patients receiving epidural analgesia should be treated with vasopressors rather than indiscriminate fluid boluses [115, 116]. Fluid deficit or overload of as little as 2.5 L [117] can cause adverse effects in the form of increased postoperative complications, prolonged hospital stay and higher costs due to increased utilisation of resources [118-120].

An excess of 0.9% saline causes hyperosmolar states, hyperchloremic acidosis [121-126], and decreased renal blood flow and glomerular filtration rate, which in turn exacerbates sodium retention. Edema impairs pulmonary gas exchange and tissue oxygenation leading to an increase in tissue pressure in organs such as the kidney which are surrounded by a non-expansible capsule. Microvascular perfusion is compromised, arterio-venous shunting increases and lymphatic drainage is reduced, leading to further edema. Hyperchloremic acidosis, as a result of saline infusions has been shown to reduce gastric blood flow and decrease gastric intramucosal pH in older adult surgical patients, and both respiratory and metabolic acidosis have been associated with impaired gastric motility. Fluid overload also causes splanchnic oedema resulting in increased abdominal pressure, ascites and even the abdominal compartment syndrome, which may lead to decreased mesenteric blood flow and ileus, with delayed recovery of gastrointestinal function, an increase in gut permeability, intestinal failure and even anastomotic dehiscence [127].

Fluid restriction resulting in fluid deficit can be as detrimental as fluid excess by causing decreased venous return and cardiac output, diminished tissue perfusion and oxygen delivery and increased blood viscosity. It can also lead to an increase in the viscosity of pulmonary mucus and result in mucous plug formation and atelectasis [128]. Induction of anaesthesia in patients with a fluid deficit further reduces the effective circulatory volume by decreasing sympathetic tone. Inadequate fluid resuscitation and decreased tissue perfusion can lead to gastrointestinal mucosal acidosis and poorer outcome.

A meta-analysis of patients undergoing major abdominal surgery has shown that patients managed in a state of near-zero fluid and electrolyte balance had a 59% reduction in risk of developing complications when compared with patients managed in a state of fluid imbalance (deficit or excess). There was also a 3.4-day reduction in hospital stay in the near-zero fluid balance group [120].

11. Inflammation and surgical outcome

The “trauma of surgery” leads to release of stress hormones and inflammatory mediators. This so-called metabolic stress is akin to the “Systemic Inflammatory Response Syndrome” (SIRS) that follows any injury or infection and is mediated by cytokines. This syndrome induces catabolism of stores of glycogen, fat and protein leading to release of glucose, free fatty acids and amino acids into the circulation – to support the process of tissue healing. It is therefore important to have sufficient protein reserves, preoperatively. This is because current thinking is that, whilst postoperative nutritional therapy may provide the energy for optimal healing and recovery, in the immediate postoperative phase it may only minimally counteract muscle catabolism, or not at all [1]. The consequences of insufficient protein reserves in the postoperative patient includes: decreased wound healing, decreased immune response, defective gut-mucosal barrier and decreased mobility and respiratory effort. All of these would lead to an overall poorer postoperative course [129].

11.1 Systemic inflammatory response (SIR)

As described in the American critical care medicine consensus [130], SIRS is described by any two of the following: a temperature >38°C (100.4°) or <36°C (96.8°F); heart rate >90 beats/min; respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg; white blood cells > 12×10^9 cells/l or < 4×10^9 cells/l or >10% immature (band) forms [130] as well as the absence of a source of an infective focus [130]. In addition to this definition there many pathophysiological changes that occur as part of the systemic inflammatory response (**Table 2)** [131].

11.2 The importance of C-reactive protein (CRP)

The prototypical marker of the systemic inflammatory response is CRP. A systematic review that explored routine clinical markers and their association to the magnitude of systemic inflammatory response after surgery – found that even though cortisol, IL-6, WCC, and CRP all peak after all types of elective operations (minor and major, laparoscopic and open), only IL-6 and CRP were consistently associated with the magnitude of the operative injury [132]. CRP is routinely measured in clinical laboratories world-wide and used extensively in clinical practice and therefore may be useful in the monitoring and modulation of the SIR after elective operation. A systematic review and meta-analysis that included 22 studies, of which 16 studies were eligible for meta-analysis, found that the pooled negative predictive value (NPV) of CRP improved each day after surgery up to 90% at postoperative day (POD) 3 for a pooled CRP cutoff of 159 mg/L [133], and concluded that infectious complications after major abdominal surgery are very unlikely in patients with a CRP below 159 mg/L on POD 3 [134]. Another systematic review and pooled-analysis evaluating the predictive value of CRP for major complications after major abdominal surgery calculated a prediction model based on major complications as a function of CRP levels on the third postoperative day [135]. Based on the model a two cut-off system was suggested consisting of a safe discharge criterion with CRP levels below 75 mg/L and above 215 mg/L serving as a predictor of complications [135].

This work highlights the clinical utility of CRP to identify the magnitude of the effect of surgery on post-operative protein catabolism and clinical outcomes. Also, CRP provides an indicator on which to judge the effect of interventions to mitigate the effects of the SIR in the post-operative period. In this context there is good evidence to support the use of laparoscopic surgery [136] and pre-operative steroids [137]. Also, there is some evidence that supports the use of pre-operative oral antibiotics in combination with mechanical bowel preparation [138, 139].

The importance of systemic inflammation and its effects on the surgical patient are summarized in **Table 3**.

12. The impact of enhanced recovery after surgery

Enhanced Recovery After Surgery (ERAS) is a relatively new pathway of care for the surgical patient [140]. It is a multi-modal, multi-disciplinary and evidence-based approach to the care, where teams of professionals work together to achieve best practice at all times, but also to be ready and able to adapt and adopt new improvements.

The first evidence-based guidance for the entire perioperative care of a patient undergoing major surgery was published in 2005 [71]. The literature showed clear evidence of benefit for avoiding bowel preparation, wound drains, nasogastric tubes, removing urinary catheters, stopping intravenous fluids early and allowing early feeding. Modern fasting guidelines allowing drinking of clear fluids two hours before surgery, and avoiding long acting premedication. Long-acting anesthetic agents and opioids for pain management should be adopted (**Figure 3**). All these treatments had good evidence for their use but were rarely practiced at that time. The evidence is constantly being updated and recommendations may change as the evidence base increases. This is exemplified by that fact that although mechanical bowel preparation on its own is of no benefit [141], the combination of oral antibiotics and mechanical bowel preparation may reduce surgical site infections and anastomotic leaks [139].

However, it was found that a protocol on its own was not enough. The care around the patients and the hospital management infrastructure needed to be organized differently [142]. First of all, there is a need to audit what is actually being done with regard to all the recommended ERAS care elements. The patient is passing through several units and different departments during the care process. In each one of these, many professionals are managing their specific focuses for the time they have the patient to care for. Once done, they pass the patient over to the next care giver. The complexity of the organization is such that no one has any overview or full control of the entire care pathway. This was a primary need that was addressed by the ERAS group by instituting audit for each and every patient. Since the patient is treated by many different professionals and they work in different parts of the hospital, it was necessary to form teams that covered all stations and all professions. This was the birth of the ERAS Team. This team is led by doctors from surgery and anesthesia who take the medical responsibility for the care that is delivered and administrated and run by nurses led by an ERAS coordinating nurse.

A major breakthrough for ERAS came in 2010 when it was reported in meta-analysis that ERAS reduced complications [143]. Now the data suggested 50% reductions in complications in colorectal surgery. This sparked a lot of interest and soon ERAS principles were employed for most major operations in randomized trials and care series, all showing similar outcomes with faster and better recovery [144]. This also held true for the most vulnerable patient groups such as the frail and older adults [145]. ERAS also reduces the impact of risk factors including diabetes [146], undernutrition [147] and facilitates optimal metabolic and nutritional care [148].

When ERAS is combined with minimally invasive surgery poor compliance to the protocol may overshadow the risks associated with co-morbidities [149]. The main mechanisms behind these improvements are likely to be associated with the marked reduction in stress reactions to the surgery, since many of the elements of ERAS have this effect [150]. In colorectal surgery, better compliance with the protocol results in shorter stay, fewer readmissions, fewer complications [151, 152] and is associated with improved 5-year survival [153].

The variation in care delivery and outcomes is huge worldwide [154], within continents (76), in countries [155] and between different practitioners [156, 157]. Much of this variation is due to the slow adoption of modern care and the practice of old and outdated care principles. The reasons for this are many, but it is interesting to find that the implementation program run by the ERAS Society has proven to work in all major continents and in different socio-economic environments. With the marked reduction in complications and the opening up of resources with faster recovery and shorter stay the economics of ERAS is positive regardless of financing of the health care system [158].

In summary, the evidence-based multi-modal and multi-professional approach to perioperative care – ERAS – has been shown to markedly improve surgical outcomes and save cost for care.

13. Recovery in the community

Following a successful perioperative hospital stay, setting of expectations and thorough preparation are key to a successful discharge from hospital including pain management, nutrition, the use of laxatives for return of bowel function, appropriate exercises to help regain normal function, and having a contact point for any questions. Information should also be provided surrounding symptoms to be wary of which may indicate the presence of a complication and what to expect in terms of follow-up. There is good evidence that nursing telephone follow-up following discharge is positive in terms of providing support and reassurance for patients [159], as well as reducing hospital readmission rates and improving patient satisfaction. The process of expectation setting commences with preoperative counselling [160] where the patient is provided information regarding what to expect on a daily basis after surgery, identifying the resources available to the patient to facilitate smooth recovery, and what the patient can do to optimize their outcome. This information giving is frequently backed up with comprehensive guides and booklets to help them better understand ERAS programs. In terms of post-discharge from hospital, support from the district nurse or home helper is invaluable in providing information regarding adequate nutrition, continued rehabilitation and exercise.

14. Postoperative nutrition

The instigation of postoperative nutrition should be a part of routine care rather than an afterthought. In addition, ensuring establishment of early oral nutrition is a fundamental tenet of ERAS [1].

The mode of nutritional delivery in the early postoperative period has been a subject of much debate, especially in procedures involving the formation of bowel anastomosis. However, several studies and systematic reviews with meta-analysis have concluded that oral and/or enteral is the preferred mode of nutrition for surgical patients. A review of five feeding routes following pancreaticoduodenectomy showed that nutritional delivery via the oral route was associated with the least complications [161]. A more recent meta-analysis using only randomized controlled trials showed enteral to be superior to parenteral nutrition following pancreaticoduodenectomy [162].

Avoidance of oral intake, which was felt to reduce the risk of complications, especially after gastrointestinal surgery involving anastomosis has not been demonstrated in the setting of any randomized controlled trials. However, this avoidance of nutritional intake carries the very real risk of postoperative underfeeding of an already at risk patient group. This could further exacerbate malnutrition and influence postoperative complication rates.

There is a distinct requirement of the understanding of this metabolic response and how to optimize or support the postoperative patient with the appropriate nutritional therapy especially in instances when the patient is malnourished. The long term caloric and protein deficits in the post-surgical patient results in poorer postoperative outcomes.

14.1 Early postoperative nutrition

Early nutrition has been shown in abdominal and pelvis surgery to stimulate peristalsis and GI excretion, reduces the risk of postoperative ileus and shortens overall hospitalization period. It was observed that patients who had earlier enteral feeding had fewer complications after colorectal surgery (4.5%) vs 19.4% late enteral nutrition [163]. A Cochrane review on early enteral nutrition also showed no difference in risk of postoperative complications in patients fed early (within 24 hours) and those fed late. Importantly they showed that patients who were fed early had a reduction in mortality RR (0.41, 95% CI 0.18 to 0.93) [164]. An updated review on the same premise found reduction in length of hospital stay but was inconclusive on postoperative outcomes and quality of life [165].

14.2 Routes of feeding

The current ESPEN guidelines state that 'Oral nutritional intake shall be continued after surgery without interruption and oral intake, including clear liquids, shall be initiated within hours after surgery in most patients' [1]. Perioperative nutritional support therapy is indicated in patients with malnutrition and those at nutritional risk. Perioperative nutritional therapy should also be initiated, if it is anticipated that the patient will be unable to eat for more than five days perioperatively. It is also indicated in patients expected to have low oral intake and who cannot maintain above 50% of recommended intake for more than seven days. In these situations, it is recommended to initiate nutritional support therapy without delay.

This is further supported by the systematic reviews and meta-analysis on several gastrointestinal surgical procedures that have shown no increased benefit of food avoidance and indeed better outcomes in the patients that received oral nutrition and those that were enterally fed [161, 164-166]. In all of these instances they found that early enteral and oral nutrition was not associated with an increase in clinically relevant complications, but rather a shorter length of hospital stay [161, 162, 165, 166]. Only in cases If the energy and nutrient requirements cannot be met by oral and enteral intake alone (<50% of caloric requirement) for more than seven days, a combination of enteral and parenteral nutrition is recommended [1].

15 Postoperative exercise intervention

Exercise stimulates muscle capillarization, protein synthesis, insulin sensitivity and mitochondrial function and proliferation, and therefore is a good strategy to maximize postoperative recovery. However, robust voluntary exercise intervention postoperatively at a time when metabolic dysregulation and fatigue are at their greatest is unlikely to be practicable, and fatigue may persist for many weeks after surgery [167]. Furthermore, muscle wasting and deconditioning will be exacerbated by prolonged periods of bed-rest [44]. In this situation, non-voluntary, transcutaneous, electrically evoked muscle contraction may be an effective strategy for the maintaining or improving muscle mass and function after surgery until voluntary exercise, which is likely to be most effective, is practicable [168]. Given muscle mass restoration following wasting is known to be slower and of less magnitude in older people [169], resistance exercise intervention in older people will need to be supervised and intensive to be successful. Patient muscle mass restoration may be augmented if exercise intervention is combined with protein nutrition, although this is controversial providing the volunteer is in protein balance[170].

16. The role of novel nutrients and substrates

In the last decades, standard enteral and parenteral formulas have been supplemented with specific nutrients and substrates with the goal of improving several metabolic pathways, which are deranged by surgical injury. The peculiar and unique mechanisms of action of some substrates, established first in experimental settings, encouraged the induction of clinical trials.

16.1 Glutamine

Glutamine is involved in a variety of biological processes, such as anabolic functions, acid-base regulation in the kidney, and ammonia metabolism [171]. Depletion in glutamine storage during stressful events [172] has been reported, and an exogenous supplementation is associated with improved protein synthesis, preservation of gut barrier, enhancement of wound healing, reduction of oxidative stress, negative nitrogen balance, improvement of glucose metabolism, and modulation of the immune system [173].

Until 2007, several randomized, but underpowered, clinical trials (RCTs) have been published and when the results were pooled in a meta-analysis [174], the effect of parenteral or enteral glutamine supplementation resulted in a significant reduction of surgical morbidity and duration of hospitalization. In 2009, the largest RCT (n=428) on the impact of the parenteral glutamine supplementation (0.4 g/kg/day) in major abdominal operations for cancer, rejected the hypothesis of a protective effect on any type of surgery-related morbidity and on the length of hospital stay [175]. More recently a multicenter double-blind RCT was reported including 150 surgical ICU patients without renal or hepatic failure, or shock. All received isonitrogenous isocaloric parenteral nutrition (1.5 g/kg/day). In the intervention group, glutamine was administered in the standard dosage of 0.5 g/kg/day. No significant differences were seen with the primary endpoints of hospital mortality and infection rate (mortality glutamine vs. standard 14.7% vs. 17.3%, bloodstream infection rate 9.6 vs. 8.4 per 1000 hospital days) [176].

A recent meta-analysis [177], included 19 RCTs with 1243 patients scheduled for elective major abdominal surgery. Glutamine supplementation did not affect overall morbidity (RR = 0.84; p = 0.473) and infectious morbidity (RR = 0.64; p = 0.087). Patients treated with glutamine had a significant reduction in length of hospital stay.

16.2 Omega-3 fatty acids

Fatty acids are potent modulators of the immune and inflammatory responses. They are incorporated into the cell membrane influencing the function and structure. By penetrating into the cell cytoplasm, fatty acids affect the synthesis of eicosanoids, cytokines and several other key mediators. Furthermore, they impact on gene expression and cell signaling. In addition, the cell-mediated immune responses are deeply affected by different type of fatty acids. Specifically, omega-3 fatty, as opposite to omega-6 acids, stimulate the synthesis of less proinflammatory leukotrienes, prostaglandins, and thromboxanes [178].

Despite the strong molecular background, robust clinical studies on the effect of parenteral formulas containing omega-3 fatty acid-based lipid emulsion are limited. The largest RCT on this topic showed no significant difference between treatment and control arms in postoperative complication rates with an associated and unexplained 5-day reduction in LOS in the group receiving omega-3 fatty acids [179]. A recent systematic review and meta-analysis collected 49 RCTs addressing the impact of omega-3 fatty acids on surgical outcomes [180], but only 24 studies, with a total of 2154 patients, reported the rate of postoperative infections. Regardless of the commercial formulation used, the risk ratio was in favor of the group receiving omega-3 fatty acids (RR=0.60; 95%CI [0.490, 0.72]). As properly emphasized by the authors, the major constraint of this meta-analysis [180], as well as others [181], was the inclusion of underpowered and non-significant trials. This limitation could have produced overstating results.

16.3 Enteral feeds containing multiple substrates

Most of the evidence suggesting that specific nutrients may modulate the clinical course of patients undergoing major operations has been produced by testing, enteral or oral formulas enriched with arginine, omega-3 fatty acids and ribonucleotides [182, 183].

The evidence has been extensively argued and reported in the 2017 ESPEN guideline on clinical nutrition in surgery [1]. The author recommendations were as follows: “peri- or at least postoperative administration of specific formulae enriched with immunonutrients should be given in malnourished patients undergoing major cancer surgery. There is currently no clear evidence for the use of these formulae enriched with immunonutrients *versus* standard oral nutritional supplements exclusively in the preoperative period”. These statements were based after the authors’ systematic search for studies and reviews published between 2010 and 2015. However, a recent focused meta-analysis on preoperative immune modulating nutrition in gastrointestinal cancer only, has demonstrated a significant reduction in infectious complications and tendency to a shorter length of stay [182].

It should be highlighted that the vast majority of the published RCTs on immunonutrition in surgical patients were conducted outside the implementation of ERAS protocols. The beneficial effect of the administration of immunonutrients, in addition to ERAS pathways has been addressed in recent multicenter Spanish RCT [184]. They studied this association in well-nourished patients undergoing colorectal resection for cancer. The findings demonstrated a decrease in the total number of complications observed in the immunonutrition treated group compared with the control group, primarily due to a reduction in infectious complications (23.8% vs.10.7%, P=0.0007). These findings look promising but necessitate future confirmations.

17. Pre-, pro- and syn-biotics in the surgical patient

Probiotics, as defined by the World Health Organisation are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. They survive transit through the gastrointestinal tract with the majority of their activity being in the colon [185]. Prebiotics are carbohydrate compounds, primarily oligosaccharides which induce growth and/or activity of selective bacterial genera in the colon [186]. Combinations of prebiotics and probiotics in a single preparation are referred to as synbiotics [185]. Current literature suggests that multispecies preparations are more effective due to better survival of the gastro-duodenal passage or greater ability to find a biological niche. However, to date, the most appropriate species of probiotic has not been described in the currently available literature.

Probiotics have been used in the treatment of several abdominal complaints. They have been shown to be useful in the treatment of gastrointestinal infections, for oral rehydration therapy in treating acute infectious diarrhea in children [187-190], traveller's diarrhea [191] and antibiotic-associated diarrhea in both children [192-194] and adults [195-198]. Recent ESPEN guidelines stated that use of a specific probiotic multi strain mixture may be beneficial for primary and secondary prevention of pouchitis in patients with UC who have undergone colectomy and ileo- anal pouch anastomosis. There are some data to confirm the use of the same multi strain probiotic mixture for the treatment of pouchitis after antibiotic treatment failure as well as for the treatment of mild to moderate ulcerative colitis [199]. The suggested mechanisms of action include both a direct antimicrobial effects as well as indirectly or competitively excluding potentially pathogenic bacteria [200]. They achieve this by producing bacteriocins which inhibit pathogenic epithelial adherence and production of virulence factor, and prevent bacterial translocation via tight junctions [200, 201]. They also alter gut microenvironment by altering the mucosal pH, which further inhibits pathogenic bacteria. Additionally, others have shown that probiotic bacteria can hamper the inflammatory response by promoting anti-inflammatory cytokine production [200, 202]. Whilst these nutritional adjuncts are emerging as potential treatments that could help reduce the incidence of postoperative infection, the success or failure of one strain cannot be extrapolated to other strains.

To the post-surgical patient, the stress of the operative procedure can lead to a proinflammatory stimulus that increases gut permeability. Increased gut permeability together with dysbiosis may lead to increased bacterial translocation across the gut barrier into the circulation. Bacterial translocation is an important pathogenic factor for the increased risk of infections. To this end the introduction of probiotics or synbiotics would be expected to maintain gut barrier function by restoring intestinal permeability ameliorating the intestinal inflammatory response and the release of cytokines, and maintaining the homeostasis of the normal gut microbiota.

A number of randomized controlled trials (RCTs) have examined the value of prebiotics and probiotics in reducing postoperative complications in particular post-operative infective complications. The interest in synbiotics, is based on emerging evidence that the proliferation of probiotic bacteria can be enhanced by the co-administration of prebiotics [203]. Indeed a more recent meta-analysis has shown that whilst infectious complications were reduced after elective abdominal surgery, the effect was better still in those patients who received synbiotics [204].

Contrastingly, some studies have yielded mixed results that probably are due to the variations of probiotics used, methodological quality and study endpoints. Additionally, others have described adverse events surrounding probiotics use. It is, however, noteworthy that serious adverse effects of probiotics are uncommon in those who are well. In patients with severe pancreatitis, administration of probiotics was associated with an increased frequency of bowel ischemia – the mechanism of this is still unexplained [205-207]. However, this effect of probiotics has not been identified in any other study. In the most recent meta-analysis [204], no serious adverse events were noted. They concluded that probiotics and synbiotics are safe in elective gastrointestinal surgery and is associated with a significant reduction in infectious complications.

18. Patient and caregiver partnership

The period surrounding a major surgical procedure is highly taxing on patients and their caregivers. Perioperative nutrition is recognized as a substantial issue, with significant weight loss not uncommon. Malnutrition in this setting is multifactorial, including issues with poor appetite, unappealing hospital nutrition, postoperative pain and a reduced level of consciousness. Support from family is frequently key to optimizing perioperative nutritional intake and modification of previous eating habits including consuming high calorie foods on a little but often basis. Oral nutritional supplementation is often met with variable patient acceptability and hence compliance is often not optimal. The effects of major surgery and indeed the complications, have wide reaching effects on not just the patient but also their families and caregivers, rendering them a bystander in the care of their loved ones. The importance of communication cannot be overemphasized in this setting, and a strong partnership between the surgeon and patient, family and caregivers is needed to overcome complicated postoperative courses.

19. Future directions for research and policy

The evidence contains many strengths, and these are reflected in high-quality guidelines surrounding perioperative nutrition [1]. However, there are still many areas of nutrition in this setting which have not yet been fully explored. An area of research development surrounds the global obesity epidemic and its link to metabolic syndrome, with more attention being directed towards a multidisciplinary approach to the management of obesity and its related diseases [208], tying together concepts such as bariatric and orthopedic surgery, geriatrics, endocrinology, psychology and psychiatry, as well as nephrology and dialysis. An area of research which is going to become increasingly relevant is the shift in population related to the ageing epidemic which is currently underway. With increasing frailty comes weight loss, progressive skeletal muscle weakness, exhaustion and inactivity, all of which increase the prevalence of disability, loss of independence and worsened clinical outcomes.

Not only are there challenges in developing an evidence base for interventions, but also in the implementation of this evidence once established. One area in which implementation lags behind the evidence base for its practice is ERAS protocols in surgery, with a multicenter qualitative study finding the main barriers to implementation being time restraints, a reluctance to change and the logistics of setup [209]. Another topic is that of fasting guidelines in enterally fed in critical care patients. Again, this identified issues surrounding mistrust of the guideline, resistance to a change in clinical practice, as well as perceived increased clinical complexity which all acted as barriers to implementation. There are some key concepts which are necessary for increasing implementation which include promotion of education including resources such as the ESPEN journal, ESPEN consensus papers, the LLL courses and live-expert courses, as well as improved communication between members of the multidisciplinary team. This may be facilitated by the creation of specialty-specific guidelines including a simplified version for community-based care as well as a patient-orientated version.

20. Conclusions

These proceedings of the ESPEN Symposium on perioperative care encompass the scientific basis of nutritional and metabolic care in the perioperative period and also suggest areas for suture research and change in policy. The main take-home messages are summarized in **Table 4**.

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Legends for Figures:

Figure 1: Prevalence of decreased eating and association with 30-day hospital mortality in preoperative, postoperative and non-surgical patients. Each dot represents 1% prevalence within the patient group. Normal eating is shown in green and is the reference category for calculation of the univariate odds ratio for death in hospital within 30 days shown as estimate with 95% confidence intervals.

Figure 2: Suggested algorithm for perioperative fluid therapy

Figure 3: Elements of Enhanced Recovery After Surgery Pathways in the pre-, intra- and post-operative periods.

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Conflicts of interest:

LG, AA, RB, KD, PLG, DHJ, SK, ZK, DCM, KER, MPS, AS and RS: None to declare

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Table 1: Definitions of Sarcopenia (taken from the Society on Sarcopenia, Cachexia, and Wasting Disorders (SCWD) website).

Definition	Function	Muscle Mass
Sarcopenia and Frailty Research Specialist Interest Group (SIG) – cachexia-anorexia in chronic wasting disease [25]	Gait speed <0.8 m/s, OR other physical performance test	Low muscle mass (2SD)
European Working Group of Sarcopenia in Older Persons (EWGSOP) [21]	Gait speed <0.8 m/s; grip strength 40 kg males, 30 kg female	Low muscle mass (not defined)
IWGS Sarcopenia Task Force [22]	Gait speed <1.0 m/s, grip strength	Low appendicular lean mass (<7.23 kg/m^2 in men, 5.67 kg/m^2 in women)
Sarcopenia with limited mobility (SCWD) [10]	6-minute walk <400 m, OR gait speed <1.0 m/s	Low appendicular lean mass/height^2
Asian Working Group for Sarcopenia [23]	Gait speed <0.8 m/s; grip strength 26 kg males, 18 kg females	Low appendicular lean mass/height^2
Foundation for the National Institutes of Health [24]	Gait speed <0.8 m/s; grip strength 26 kg males, 16 kg females	Appendicular lean mass/BMI

Table 2: Pathophysiological changes of the systemic inflammatory response

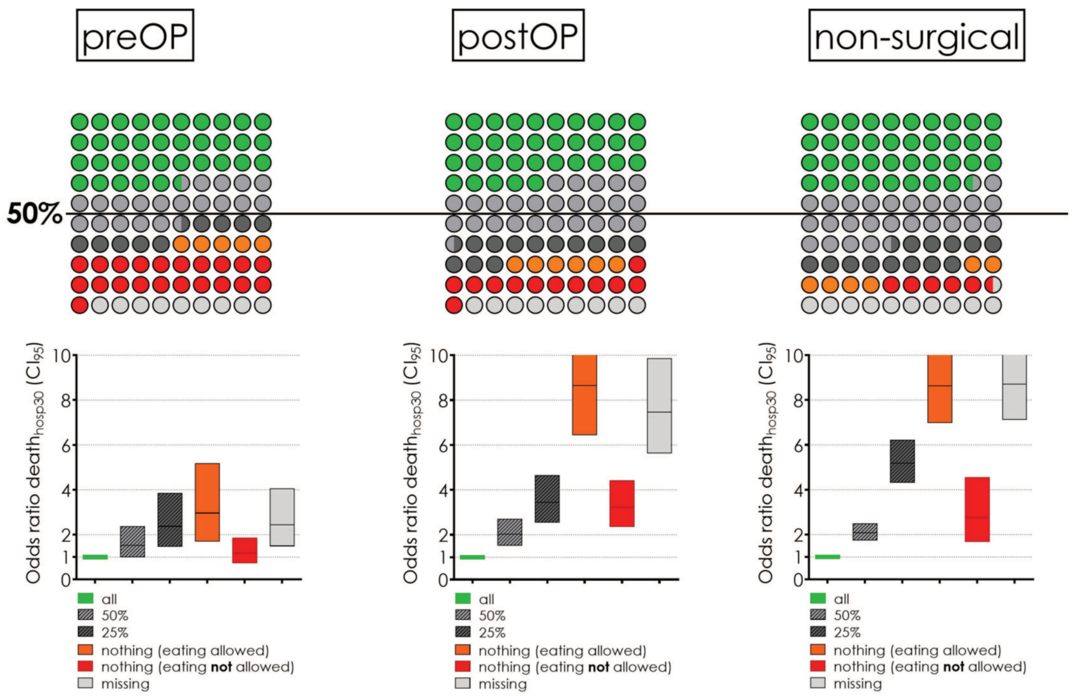
Neuroendocrine changes
Fever, somnolence, fatigue and anorexia
Increased adrenal secretion of cortisol, adrenaline and glucagon
Hematopoietic changes
Anemia
Leucocytosis
Thrombocytosis
Metabolic changes
Loss of muscle and negative nitrogen balance
Increased Lipolysis
Trace metal sequestration
Diuresis
Hepatic changes
Increased blood flow
Increased acute phase protein production

Table 3: Systemic inflammation and its effects on the surgical patient

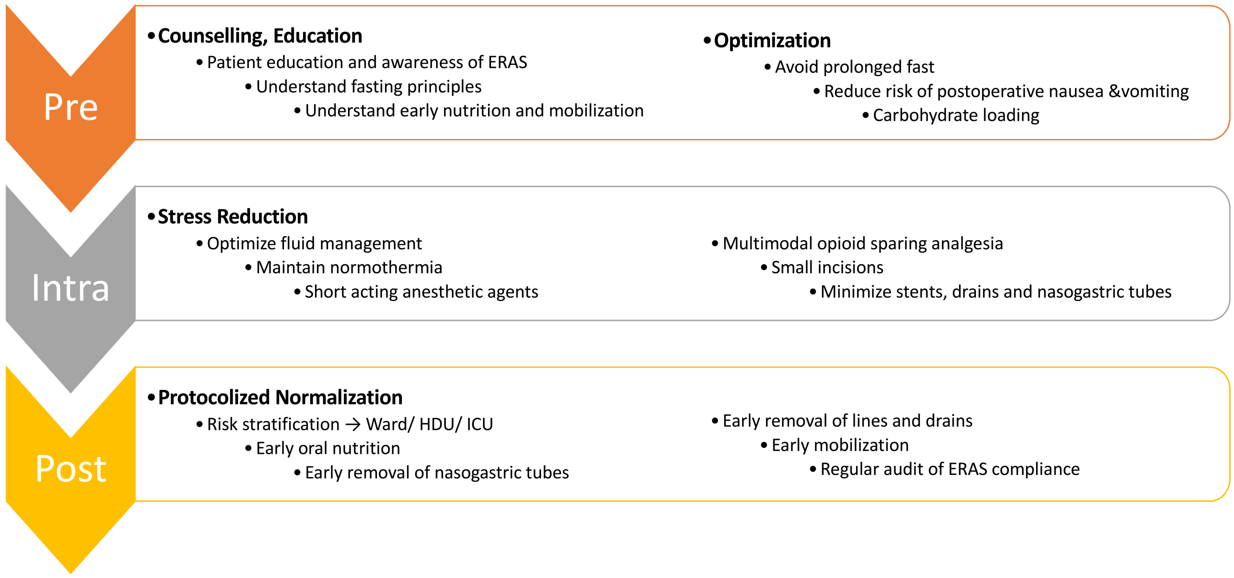
Protein catabolism after surgery leads to depletion of lean mass.
The magnitude of the post-operative systemic inflammatory response corresponds to the amount of surgical trauma.
The higher the response is associated with poorer surgical outcome.
C-reactive protein is useful in quantifying the magnitude of the post-operative systemic response.
Moderating the post-operative systemic inflammatory response (example by using a laparoscopic approach) - appears to improve surgical outcome.

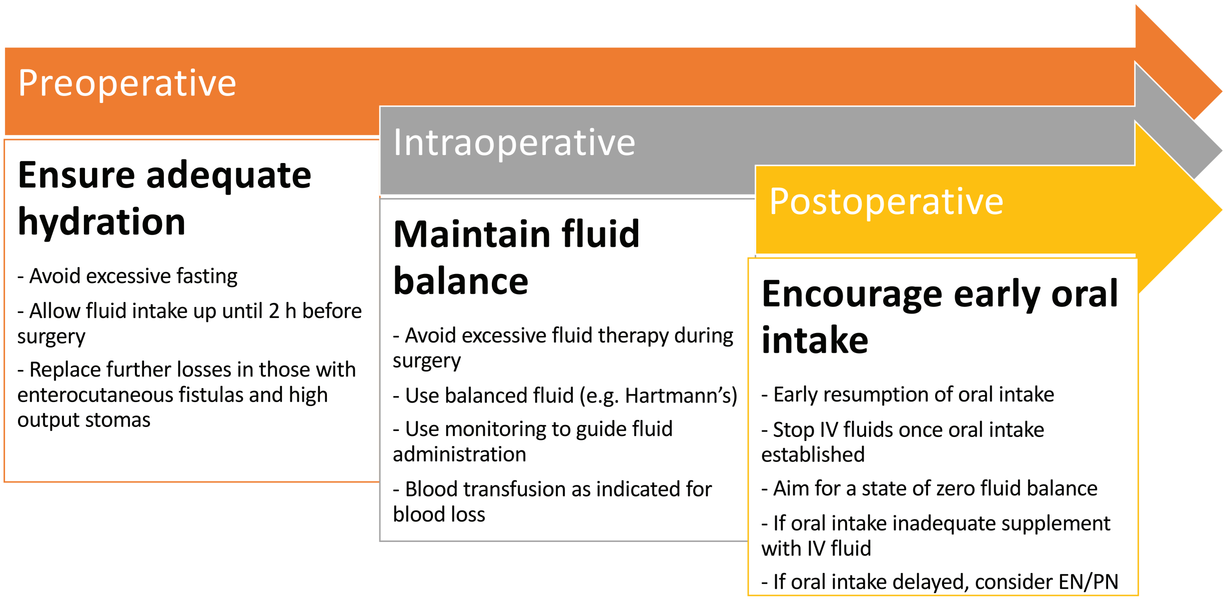
Table 4: Take home messages

- History is continuity – those who don't learn from the lessons of history are condemned to repeat it.
- Preoperative muscle mass is critical to postoperative outcome.
- Sarcopenic obesity is an independent predictor of postoperative complications, especially when the host genotype is associated with weight loss and a low skeletal muscle index.
- Surgical patients who don't eat when eating is allowed and an increased length of stay when compared with those who are not allowed to eat.
- Nutritional risk score (NRS) is validated for surgical patients and should be performed at least 10 days before surgery.
- The perioperative period should be used for conditioning regimens like prehabilitation.
- High blood glucose concentrations in patients who were normoglycemic previously are associated with increased postoperative complications.
- Excess 0.9% saline is detrimental in the perioperative period and salt and water overload of >2.5 L is associated with adverse outcome.
- Enhanced Recovery After Surgery principles are appropriate for all patients, but good results are dependent on a challenging inter-disciplinary cooperation to ensure high compliance rates.
- Inflammation is a marker for surgical complications and CRP profiling is useful.
- The effects of nutrients are dissociated from nutrition and there is a role for pharmaconutrition.
- Dysbiosis contributes to inflammation – the effects of pre-, pro- and synbiotics depends on species, strains and adjuncts.
- Postoperative fatigue inhibits voluntary exercise, immobilization induces anabolic resistance, and the lower the anabolic response to feeding, the higher the muscle loss.
- Perioperative nursing in the hospital and community after discharge is a key component for good outcome.
- A strong partnership between the surgeon and patient/family/caregivers is needed to overcome complicated postoperative courses.



preOP
postOP
non-surgical
50%
Odds ratio death$_{hosp30}$ (CI$_{95}$)
all
50%
25%
nothing (eating allowed)
nothing (eating **not** allowed)
missing


Pre
• Counselling, Education
• Patient education and awareness of ERAS
• Understand fasting principles
• Understand early nutrition and mobilization
• Optimization
• Avoid prolonged fast
• Reduce risk of postoperative nausea &vomiting
• Carbohydrate loading
Intra
• Stress Reduction
• Optimize fluid management
• Maintain normothermia
• Short acting anesthetic agents
• Multimodal opioid sparing analgesia
• Small incisions
• Minimize stents, drains and nasogastric tubes
Post
• Protocolized Normalization
• Risk stratification → Ward/ HDU/ ICU
• Early oral nutrition
• Early removal of nasogastric tubes
• Early removal of lines and drains
• Early mobilization
• Regular audit of ERAS compliance



Preoperative
Ensure adequate hydration
- Avoid excessive fasting
- Allow fluid intake up until 2 h before surgery
- Replace further losses in those with enterocutaneous fistulas and high output stomas
Intraoperative
Maintain fluid balance
- Avoid excessive fluid therapy during surgery
- Use balanced fluid (e.g. Hartmann's)
- Use monitoring to guide fluid administration
- Blood transfusion as indicated for blood loss
Postoperative
Encourage early oral intake
- Early resumption of oral intake
- Stop IV fluids once oral intake established
- Aim for a state of zero fluid balance
- If oral intake inadequate supplement with IV fluid
- If oral intake delayed, consider EN/PN