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REVIEW ARTICLE

Preoperative optimization for major hepatic resection

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Abstract
Purpose Major hepatic resections are performed for primary hepatobiliary malignancies, metastatic disease, and benign lesions. Patients with chronic liver disease, including cirrhosis and steatosis, are at an elevated risk of malnutrition and impaired strength and exercise capacity, deficits which cause increased risk of postoperative complications and mortality. The aims of this report are to discuss the pathophysiology of changes in nutrition, exercise capacity, and muscle strength in patient populations likely to require major hepatectomy, and review recommendations for preoperative evaluation and optimization.
Methods Nutritional and functional impairment in preoperative hepatectomy patients, especially those with underlying liver disease, have a complex and multifactorial physiologic basis that is not completely understood.
Results Recognition of malnutrition and compromised strength and exercise tolerance preoperatively can be difficult, but is critical in providing the opportunity to intervene prior to major hepatic resection and potentially improve postoperative outcomes. There is promising data on a variety of nutritional strategies to ensure adequate intake of calories, proteins, vitamins, and minerals in patients with cirrhosis and reduce liver size and degree of fatty infiltration in patients with hepatic steatosis. Emerging evidence supports structured exercise programs to improve exercise tolerance and counteract muscle wasting.
Conclusions The importance of nutrition and functional status in patients indicated for major liver resection is apparent, and emerging evidence supports structured preoperative preparation programs involving nutritional intervention and exercise training. Further research is needed in this field to develop optimal protocols to evaluate and treat this heterogeneous cohort of patients.

Keywords Major hepatectomy · Preoperative nutrition · Exercise capacity

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Importance of nutrition in major abdominal surgery

The importance of nutrition in all major surgery is now apparent, and it is accepted that assessment of nutritional status and intervention if indicated is essential in the pre- and postoperative periods [1]. More than 40% of surgical patients suffer from malnutrition [2] and there is a clear correlation between malnutrition and an increase in postoperative complications including morbidity, mortality, overall and surgical site infections, and increased length of [2–7]. The most recent set of European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines state that nutrition is critically important to recovery from major surgery, and patients at a high risk due to impaired nutritional status should ideally receive oral supplementation prior to major surgery, even if this results in the delay of resection of a malignancy [1]. Early consultation of a dietician may be indicated, and attempts should be made to provide preoperative nutritional therapy before hospital admission when feasible [1]. Oral nutrition intake is greatly preferable, and a study of patients with gastroesophageal, pancreatic, and colorectal cancers demonstrated a significant decrease in postoperative infections and length of hospital stay in patients who received 5 days of oral supplemental nutrition before surgery [8].

The primary goals of preoperative nutritional therapy should be to prevent the loss of lean body mass and provide adequate support for postoperative wound healing. There is also emerging data regarding the importance of immunomodulation in surgery particularly for malignancies to optimize long-term outcomes [4, 9, 10]. Many, but not all, recent studies support the use of immune-modulating nutritional supplementation including arginine and ω3 fatty acids in the perioperative period [4, 11].

It is important to acknowledge the increasing prevalence of obesity worldwide because of the unique nutritional risks. Obesity is a disease of macronutrient excess but is commonly associated with micronutrient deficiencies including thiamine and vitamin D [11–13] and decreased lean muscle mass [14]. In a recent study of 4652 people over the age of 60 in the USA, the prevalence of sarcopenic obesity was 18% in women and 43% in men [15]. There is a clear association of sarcopenic obesity with perioperative morbidity, and cancer patients with sarcopenic obesity have an elevated risk of chemotherapy toxicity and overall mortality [16]. These patients should be counseled regarding their increased perioperative risk, and ideally undergo modifications of diet and activity level before major surgery.

In conjunction with the recognition of the importance of longer term preoperative nutrition, the traditional practice of fasting after midnight prior to surgery has been challenged. A recent review of 38 randomized, controlled comparisons within 22 trials found no evidence to support the standard "nil by mouth from midnight" (NPO) preoperative fasting policy, and in fact suggested that consumption of water preoperatively resulted in decreased gastric volumes [17]. Particularly in the case of patients with underlying liver disease and its associated metabolic alterations, NPO time should be limited (except in cases of variceal bleeding or severe hepatic encephalopathy). This recommendation is in line with the ESPEN guidelines to allow intake of solid food until 6 h preoperatively and clear fluids until 2 h before anesthesia (Table 1) [1].

Table 1 ESPEN guidelines adapted for hepatic surgery [1]

Preoperative
- All patients: assess nutritional status of all patients: BMI (< 18.5%), recent weight loss (> 10–15% in prior 6 months), albumin (< 30 g/L), and SGA (grade C) indicate severe risk
- Patients with severe nutritional risk: provide 7–14 days of immunomodulating nutritional supplementation even if resection of malignancy is delayed
- Consider Dobhoff tube placement
- Avoid parenteral nutrition whenever possible
- Patients without severe nutritional risk: if energy needs not met by food provide oral nutritional supplementation
- All patients: allow clear fluids until 2 h before anesthesia, solid foods until 6 h before

Intraoperative
- Place Dobhoff tube if patient unlikely to advance to full enteral nutrition postoperatively

Postoperative
- All patients: initiate enteral feeding within 24 h of surgery, including tube feeds in patients with severe nutritional risk or anticipated inadequate oral intake
- All patients: continue regular reassessment of nutritional status

Unique nutritional considerations in hepatic resections

Introduction to nutrition and hepatic resection

The increased understanding of the importance of nutritional status in all abdominal surgery is particularly relevant in the subset of patients who are indicated for liver surgery. Hepatic resection is indicated for a variety of benign and malignant diseases including hepatocellular carcinoma (HCC), cholangiocarcinoma, gallbladder carcinoma, rare primary hepatobiliary malignancies, metastases from colorectal cancer and other primary malignancies, and benign pathology [18]. Much of the literature on preoperative optimization for hepatic surgery focuses on patients with cirrhosis awaiting liver transplant, but these principles can be extrapolated to partial hepatic resections as well as other patient populations and surgical indications. Liver resection for living-liver donation for transplantation is another indication for major hepatectomy; however, this procedure is limited to exceptionally healthy individuals who tend to have normal preoperative nutritional and functional statuses [19].

The clinical success of a major hepatic resection depends on the ability of the remnant liver to regenerate via hyperplasia. The mortality of posthepatectomy liver failure is over 60% despite a decrease in posthepatectomy mortality rate to less than 5% in patients without underlying liver [20, 21]. Underlying liver pathology and systemic conditions including malnutrition affect the rate of regeneration following hepatectomy; therefore, nutritional evaluation is essential in determining the regeneration potential of the remaining liver and thus the safety of the resection [19]. A recent review noted malnutrition as a risk factor for postoperative liver failure following hepatic resection for all indications, likely due to a combination of immune impairment, decreased hepatic protein synthesis, and diminished ability of the liver to regenerate [5, 22, 23]. There is unique underlying pathophysiology and perioperative risk in patients with HCC in the setting of underlying cirrhosis compared to patients with malignancy associated with hepatic steatosis and these populations warrant separate discussion.

Resection of hepatocellular carcinoma in patients with cirrhosis

Prevalence of nutritional impairment

HCC is the second largest cause of cancer mortality worldwide and projected to rise from seventh to third great cause of cancer mortality in the USA over the next 15 years [24–27]. Mortality from HCC is increasing in the USA and Canada due to the high prevalence of hepatitis C and spread of nonalcoholic fatty liver disease [28]. Current guidelines [29, 30] recommend resection for BCLC stage A (single or up to three nodules ≤ 3 cm with Child-Pugh A-B and Performance Status 0). Recent reports from Asia have described a survival advantage associated with resection even in selected patients with advanced-stage tumors [31–33].

The most significant risk factor for HCC is cirrhosis [29] and malnutrition is found in 50–90% of patients with obstructive jaundice or moderate to severe cirrhosis [34–37]. It is one of the most important prognostic factors in end-stage liver disease overall [38] and associated with increased morbidity and mortality in the absence of major surgery [36, 39, 40]. Even in patients with CTP class A or B, the prevalence of malnutrition is as high as 25–46 and 84%, respectively [41, 42]. Protein depletion is more common in male patients for unclear reasons and in patients with alcoholic liver disease [43]. Malnutrition is even more relevant in patients with cirrhosis who require major hepatectomy due to the interplay between nutritional status, hepatic regeneration, and wound healing. Nutritional therapy for patients with liver disease undergoing hepatic and other abdominal surgeries has been proven to improve postoperative outcomes [22, 44].

Pathophysiology of nutritional deficiency

The etiology of malnutrition in patients with underlying liver disease is multifactorial. A hypermetabolic state (defined as a 120% increase in resting energy expenditure) is present in 4–34% of cirrhotic patients without association with gender, etiology, or severity of liver disease, hepatic malignancy, or presence of ascites [38, 43, 45, 46]. Cirrhosis causes hyperdynamic circulation via increased sympathetic nervous system activity, leading to systemic vasodilatation, expanded intravascular blood volume, and greater energy requirement. Complications of cirrhosis including spontaneous bacterial peritonitis, sepsis, and fever of unknown origin can also drive increases in metabolic demand and protein catabolism [34, 47].

Despite these elevated protein and calorie requirements, cirrhosis is often associated with an unintentional decrease in nutrient intake and impaired nutrition absorption and utilization. Loss of appetite can be related to alcohol-related anorexia [34], elevated cytokines tumor necrosis factor α and leptin [48], changes in ghrelin levels [34], and mechanically impaired gastric expansion due to ascites [49]. Patients with cirrhosis, particularly those with ascites, frequently report nausea, bloating, and abdominal discomfort contributing to decreased tolerance of oral intake [36, 50]. Sodium restriction required for control of peripheral edema and ascites may make the recommended diet unappealing [37]. Additionally, during hospitalizations, patients are frequently fasted in anticipation of procedures and, otherwise, do not have access to foods they find appealing [49]. Patients with cirrhosis are often placed on a low-protein diet to minimize the risk of hepatic encephalopathy, which further impairs nutritional status and wound healing potential following major surgery [49]. Protein loss in cirrhosis can result from other iatrogenic causes as well including repeat paracenteses for symptomatic relief of ascites, or due to blood loss from esophageal or gastric varices or intestinal ulcerations which may be occult [38, 47].

Portal hypertension and subsequent portosystemic shunting result in nutrients bypassing metabolic processing in the liver, impairing digestion and absorption [34, 49]. Related conditions including pancreatic insufficiency, mucosal congestion, and atrophy of small intestine villi can exacerbate the inadequate absorption and utilization of vitamin nutrients. Lactulose, a commonly prescribed disaccharide cathartic, is not absorbed in the small intestine but potentially alters the bacterial flora, and may affect absorptive capacity [47].

Perpetuating the consequences of nutrient malabsorption, cirrhosis causes intrinsic alterations in the liver's capacity for glucose metabolism, protein synthesis, and glycogen storage. Hepatocytes are unable to store, synthesize, and metabolize glycogen, leading to a premature switch gluconeogenesis from fats and proteins after as little time as an overnight fast [47, 51, 52]. In patients with cirrhosis, serum insulin levels are higher in both fasted and post-prandial states which decreases peripheral glucose metabolism [36, 53]. Polyunsaturated fatty acid (PUFA) deficiency is seen in cirrhosis due to decreased hepatic synthesis from essential fatty acid precursors, although potential benefits of supplementation are unclear [37].

Branched-chain amino acids (BCAAs) leucine, isoleucine, and valine cannot be synthesized, must be obtained from the diet, and are predominantly metabolized by muscle. Patients with cirrhosis and decreased lean muscle mass have a deficiency of BCAAs, leading to amino acid imbalance and subsequent alteration of brain ammonia levels [54, 55]. Deficiencies of magnesium, sodium, phosphorus, and zinc also occur with liver disease, and due to iatrogenic causes like the use of diuretics [34, 38, 45]. Zinc deficiency perpetuates the damage by causing impaired appetite and taste, and altered protein metabolism [56]. Hundreds of metalloenzymes require zinc, including RNA and DNA polymerases, and zinc is sequestered in wounds, exacerbating any existing deficiency at the time of operation [5].

Cholestatic liver disease, seen in cirrhosis as well as extrahepatic cholangiocarcinomas, can cause impaired absorption

of fat-soluble vitamins A, D, E, and K via abnormally low intraluminal bile salt concentrations [56]. Deficiencies of vitamins A and D are the most common, with 92% of cirrhotic patients having some degree of vitamin D deficiency and 29% having severe deficiency (< 17.5 nmol/L) [57]. Alcoholic cirrhosis is associated with water-soluble vitamin (B complex and C) and thiamine deficiency, but these deficiencies may be seen in other forms of chronic liver disease as well [37]. Vitamin C deficiency is particularly dangerous because it is essential to the function of proline and lysine hydroxylases in wound healing [5].

Although patients at the severe end of the spectrum of cirrhosis may not be operative candidates for resection of hepatic malignancies, it is clear from these data that even patients with less severe liver disease clinically are at a high risk of compromised nutrition and deficiencies in protein and other key contributors to postoperative wound healing.

Evaluation of nutritional status

While CTP score and MELD scores are helpful for quantifying the severity of liver disease, the assessment of nutritional status in patients before major hepatectomy can be challenging. The Subjective Global Assessment (SGA) uses data from clinical history and physical examination including recent weight loss, changes in oral intake, presence of gastrointestinal symptoms, functional capacity, signs of muscle wasting, presence of peripheral edema, and metabolic demands to categorize patients as well nourished, moderately malnourished, or severely malnourished [2, 58] and has been validated in chronic liver disease [59, 60].

The ESPEN guidelines [61] recommend combining SGA with anthropometric parameters including mid-arm muscle circumference (MAMC) or mid-arm circumference (MAC) and triceps skin fold thickness (TST) in all patients with liver cirrhosis or alcoholic steatosis. Malnutrition is diagnosed if MAMC/MAC or TST is below the 5th percentile in patients 18–74 years old or 10th percentile in patients over 74 years old [39]. Both SGA and the anthropometric parameters have the advantage of not being altered by the presence of ascites or peripheral edema [47]. For pretransplant or abdominal surgical patients, the ESPEN guidelines recommend the use of phase angle or body cell mass measured by bioelectric impedance to quantify malnutrition, although these measurements are less reliable in patients with ascites [45, 61, 62].

In terms of clinical scoring systems, the Prognostic Nutritional Index (PNI) stratifies patients based on the presence or absence of an inflammatory response as indicated by serum albumin level and lymphocyte count. A low PNI has been found to be an independent predictor of poor overall survival in patients with HCC, in general [63], and HCC patients who undergo surgical resection [64, 65]. Recognizing the importance of immune-nutritional status for survival in HCC, another study [66] proposed the use of the controlling nutritional status (CONUT) score, previously validated in patients undergoing resection of colorectal cancer [67], as a prognostic factor in HCC patients undergoing hepatectomy. The score is an assessment of degree of undernutrition based on albumin, total lymphocytes, and total cholesterol [68]. The high CONUT score group was found to have a lower 5-year recurrence-free survival and overall survival rate compared to the low CONUT score group, which remained significant in multivariate analysis. CONUT score was also found to correlate with prothrombin time, Child-Pugh score of A or B vs C, and stage of hepatic fibrosis [66]. The validation of this score in other populations of patients with malignancies makes it generalizable to all patients indicated for major hepatectomy [67].

BMI can be a reliable predictor of malnutrition if the cutoff values are adjusted for severity of ascites [39], and Lee 2016 [33] demonstrated that the combination of low BMI (< 25) and low total cholesterol (< 200 mg/dl) were predictive of significantly lower recurrence-free survival and overall survival in HCC patients following surgical resection. These data suggest that BMI, albumin level, lymphocyte count, and serum cholesterol level may have prognostic value in the preoperative assessment of major hepatectomy patients. Prior research demonstrated that a larger number of comorbid factors, advanced age, and presence of symptomatic liver cirrhosis significantly predicted 30-day postoperative mortality in multivariate analysis of a European population [69].

Recommendations for preoperative nutritional intervention

In HCC patients undergoing major hepatic resection with curative intent, nutritional optimization is crucial for surgical recovery and long-term survival [70]. In general, patients with cirrhosis should take in 35–40 kcal/kg per day including 1.2–1.6 g/kg of protein [38, 61], and low-grade hepatic encephalopathy (grades I and II) should not be an indication for protein restriction [61]. Because patients with cirrhosis go into a fasting state overnight (compared to the 3 days it takes healthy individuals to have the same metabolic responses), they should receive a late evening snack to avoid the onset of gluconeogenesis [51, 52, 71]. One randomized controlled trial demonstrated significant increase in total body protein at 3, 6, and 12 months with nighttime supplementary nutrition compared to equivalent daytime supplementation [72].

Despite the 40–50% frequency of comorbid diabetes mellitus in patients with end-stage liver disease, carbohydrate intake should not be restricted, and carbohydrates should be included in 4–7 daily meals [47, 73]. On the contrary, increased fat intake in the setting of abnormally low release of hepatic VLDL can increase fat storage and exacerbate hepatic inflammation and fibrogenesis [47]. Vitamin supplementation is not routinely recommended, but is clearly indicated in the setting of a symptomatic deficiency, and if there is any

suspicion for subclinical vitamin C or D deficiency [5, 47]. Patients with alcoholic cirrhosis are at an increased risk of pancreatic insufficiency, and supplemental pancreatic enzymes should be provided [37].

Patients who cannot meet their caloric and protein goals may benefit from preoperative supplementary enteral feeding, often with an increased protein or concentrated high energy formula [47, 61]. Hemorrhage from esophageal or gastric varices due to nasogastric tube placement is a concern, but overall, the nutritional benefits outweigh the risks [37]. In rare circumstances, patients with recurrent aspiration events, uncontrolled emesis, or diarrhea may be considered for parenteral nutrition but this should not be given routinely due to the associated risks of fluid overload and sepsis, and loss of the intestinal mucosal benefits of enteral feeding [47].

Supplementation with the oral branched-chain amino acids (BCAAs) leucine, isoleucine, and valine has been recommended in for patients with hepatic encephalopathy and intolerance of enteral feeding despite treatment [37, 61], although a recent review failed to demonstrate a change in mortality, quality of life, or nutritional parameters [74]. Excitingly, new data shows oral supplementation with BCAAs before treatment improves liver function after radiofrequency ablation [75, 76] and transcatheter arterial chemoembolization [77]. In a randomized prospective study, BCAA supplementation reduced early recurrence after hepatectomy for HCC although there was no difference in overall survival in this study [78].

One recent clinical trial on immunonutrition hepatic surgery divided 26 patients into two groups: one was given IMPACT, containing ω3 fatty acids, arginine, and nucleic acids, and half-portion hospital meals and compared to a group of patients who received normal hospital meals. The immunonutrition patients had significantly lower inflammation markers including white blood cells and interleukin-6, and slightly lower aspartate aminotransferase and alanine aminotransferase level, without a difference in complications or length of stay [79]. This was the first study on immunonutrition specifically in patients undergoing surgery for hepatic malignancies and proves that immunonutrition in this population warrants further investigation.

Another emerging topic in surgical nutrition is the use of synbiotics, and initial results in liver transplant patients showed promising results with synbiotics reducing the rate of postoperative complications compared to patients who underwent selective bowel decontamination [80] or fiber only [81]. These results were replicated in 61 patients with cirrhosis undergoing liver resection who received symbiotic supplementation for 14 days preoperatively and 11 days postoperatively and demonstrated a reduced rate of infectious complications and a negative correlation with levels of serum interleukin-6 and C-reactive protein [82]. The formula used in this study was a combination previously shown to reduce postoperative infections in biliary cancer surgery patients [83, 84]: probiotics *Bifidobacterium breve* strain Yakult and *Lactobacillus casei* strain Shirota with prebiotic galactooligosaccharides. Synbiotics are an exciting area of emerging research in surgical nutrition and are recommended in the perioperative period for patients with nutritional impairment undergoing major cancer surgery [1].

Enteral nutritional support in the postoperative period

Despite the most meticulous attention to preoperative nutritional status and attempts at supplementation, the reality is that the vast majority of patients with cirrhosis who undergo liver resections experience some degree of postoperative hepatic decompensation, usually associated with hyperbilirubinemia and ascites. While an extensive discussion of postoperative nutrition is beyond the scope of this review, the importance of enteral nutrition in these patients must be emphasized. Total parenteral nutrition (TPN) is well known to be associated with metabolic and infectious complications in a population already at elevated risk of these issues. A recent systematic review identified five randomized prospective trials on enteral versus parenteral nutrition following hepatectomy and found that enteral nutrition associated fewer wound infections and catheter-related complications than parenteral nutrition [85]. For these reasons, Dobhoff feeding tube placement should be performed at the time of surgery, and tube feeding initiated within 24 h of surgery per the ESPEN guidelines in patients who are anticipated to have inadequate oral intake for at least 7 days following surgery or are unable to consume or unsafe for oral nutrition [1]. Surgical feeding access, including gastrostomy and jejunostomy tubes, can be fraught with ascitic leaks and should be avoided in this population unless absolutely necessary. As stated previously, perioperative symbiotic supplementation decreased infectious complications in this patient population and should be considered in the postoperative period [82].

Resection of metastatic disease

In North American and European populations, metastatic disease, most commonly colorectal cancer, is the most common indication for hepatectomy [18]. Colorectal cancer is the second most common cause of cancer-related death in these regions [86], and approximately half of colorectal cancer patients develop liver metastases for which hepatectomy is the optimum treatment. As expected, the threat of postoperative liver failure in this population is low (approximately 10%); however, when it occurs, it contributes dramatically to postoperative mortality rate [87].

There may be no clinical evidence of liver dysfunction in patients with metastatic disease, but preoperative assessment of nutritional and functional status remains important in the

setting of advances in knowledge about nutritional status in hepatectomy [23, 69] and abdominal surgical outcomes in general. In patients with cirrhosis, functional reserve of the liver has been a useful predictor of postoperative outcomes; however, in patients with metastatic disease in an otherwise healthy liver, hepatic reserve does not predict postoperative morbidity or mortality [69]. One study found that 38% of patients with advanced colorectal cancer have severe nutritional compromise, as identified by a patient-generated global assessment score (PGSGA) of ≥ 9 [88]. The SGA is useful for patients who require hepatectomy for metastatic or benign disease as well.

Steatosis due to obesity and chemotherapy

Patients at risk for hepatic steatosis due to obesity or preoperative chemotherapy warrant particular attention due to the associated increase in rate of postoperative complications. Hepatic steatosis is an accumulation of lipids within the liver due to obesity, alcohol use, diabetes mellitus, and other toxins, and is pathologic when the hepatic fat content is greater than 5% of the liver wet weight [21]. The most severe form is steatohepatitis in which the liver demonstrates fat infiltration, lobular inflammation, and ballooning hepatocytes progressing to fibrosis, likely via increased oxidative stress and peroxidation of lipids [21, 89]. Approximately 20–40% of the people in western countries are affected by hepatic steatosis with even greater prevalence (30–50%) in patients undergoing hepatic resection for metastatic disease [90, 91]. Both steatosis and steatohepatitis are proportional to BMI [90, 92] in surgical populations; however, 10–20% of lean patients suffer from steatosis [21].

Steatosis and particularly steatohepatitis have the potential to increase the risk of complications and mortality in major hepatectomy via multiple mechanisms [21, 93–96]. Ischemia/reperfusion injury is the major cause of damage to the remaining hepatic parenchyma during liver resection. Data from animal studies suggests that steatosis decreased total and microcirculatory blood blow, decreasing total reperfusion and leading to ongoing chronic hypoxia. This contributes to imbalances of energy homeostasis and Kupffer cell dysfunction causing an intensified inflammatory response and increased damage to hepatocytes. Additionally, steatosis impairs hepatic regeneration, likely via disturbances of cell cycle progression, and is associated with insulin resistance, which may be associated with an increased risk of postoperative wound infections [21].

Histopathologic analysis of multiple liver biopsies is the gold standard for diagnosing steatosis. There is data that computed tomography and ultrasound imaging can be used for diagnosis and monitoring of steatosis-induced hepatomegaly [97, 98]; however, there is clearly a need for more sensitive noninvasive diagnostic techniques to evaluate patients preoperatively.

Particularly relevant to patients with metastatic liver disease is the inconsistent evidence that chemotherapy may cause steatosis and steatohepatitis and adversely affect postoperative outcomes of hepatic resection. In the literature regarding colorectal cancer metastatic to the liver, there are conflicting results with regard to the type and duration of chemotherapy and associated liver injury and postoperative outcomes. One report found an association of steatohepatitis with BMI, but not with chemotherapy, although hepatic vascular injury patterns were significantly associated with oxaliplatin regimens without a change in morbidity [99]. On the contrary, another study demonstrated that ≥ 6 cycles of oxaliplatin-based chemotherapy increased the rate of hepatic sinusoidal injury, leading to decrease in functional hepatic reserve and elevated complication rate [100]. This was supported by a report demonstrating an association of oxaliplatin with sinusoidal dilation and irinotecan with steatohepatitis compared with no chemotherapy. In this group, patients with steatohepatitis were at an elevated risk of 90-day mortality [101]. Another report found a significantly elevated risk of steatosis (> 30%) with irinotecan chemotherapy compared to no chemotherapy, 5-fluorouracil, or oxaliplatin without a difference in short-term mortality [102]. A more recent study corroborated these results, noting that irinotecan chemotherapy, elevated BMI, and diabetes mellitus were associated with steatosis and steatohepatitis but chemotherapy did not increase the risk of liver-related complications [103].

Additional research has demonstrated a difference in elevated rate of steatosis in patients who received preoperative chemotherapy of any type compared to patients who did not receive chemotherapy, but this did not result in a difference in short-term clinical outcomes [104], or no differences in outcomes or presence of steatosis in patients who were treated with preoperative chemotherapy [105]. Additional investigations found a higher incidence of morbidity [106, 107] including postoperative liver failure [87] in patients who received preoperative chemotherapy in correlation with the number of cycles but not the type of chemotherapy [106]. Until there is a more definitive consensus in the literature, decisions regarding neoadjuvant therapy in this patient population should be made based on multidisciplinary consultation and attention to individual patient risks of steatosis, balanced with the fact that liver resection is usually the only option for definitive cure in these patients [108].

Recommendations for the treatment of obesity-related steatosis

Given the modern prevalence of obesity and recent advances in understanding the relationship between obesity, steatosis, and underlying metabolic derangements [12], obese patients

in particular warrant nutritional evaluation and optimization. An early study from Japan on obesity-related hepatic steatosis demonstrated a significant reduction in mean liver volume after 3 months on a low-calorie diet [97], supporting the reversible nature of this disease [109]. Another study using ultrasound for assessment of liver size demonstrated a significant decrease in hepatomegaly following 2 weeks on a very low-calorie diet in 50 morbidly obese patients indicated for bariatric surgery, although degree of steatosis was not assessed directly [98]. In a more recent report of 111 patients undergoing major hepatic resection, just 1 week of dietary calorie and fat restriction was associated with decreased hepatic steatosis, a reduction in steatohepatitis, and decreased postoperative blood loss [90]. These exciting results indicate that even short-term preoperative dietary modifications can have a clinically significant impact on outcomes. Further investigation in dietary intervention to reduce steatosis in at-risk populations is warranted and has the potential to decrease postoperative complications and improve outcomes for these patients.

Physical condition

Compromised exercise capacity in patients with cirrhosis

Introduction and pathophysiology of impairment

The interplay between nutritional and functional status is complex, particularly in patients with malignancies or other underlying chronic diseases. Cirrhosis is clearly associated with increased fatigue and muscle wasting [110], and physical fitness has been shown to affect outcomes of liver transplant and survival in patients with cirrhosis. The term "physical fitness" includes the physiologic parameters of body composition, muscle strength, flexibility, and exercise capacity, which is the ability to consume and utilize oxygen during aerobic exercise [110]. The standard measurement of exercise capacity is maximal oxygen consumption (VO_{2max}) which is obtained by quantifying oxygen content of expired air during an exercise test to exhaustion [110]. Muscle strength, essential for independent functioning and recovery from major surgery, naturally declines with age. It can be measured by knee flexion and extension and grip strength, although the values obtained can vary with gender, age, height, and weight [111].

A recent review evaluated 11 studies on the exercise capacity of patients with cirrhosis without other significant comorbidities, and all reports found decreased exercise capacity compared to healthy controls or predicted values [110]. Severity of liver disease as quantified by CTP score was found to have a negative correlation with VO_{2peak} in some reports [112–115] but not others [116, 117]. Exercise capacity has been shown to correlate with mortality in patient with cirrhosis both without liver transplant and postoperatively following transplant [118, 119].

Four reports have examined muscle strength in patients with cirrhosis without additional medical problems, and two found diminished strength compared to healthy [115, 117, 120, 121]. Interestingly, in the two studies that stratified patient by CTP scores, no difference was found [117, 120], suggesting that sarcopenia may depend more on overall nutritional status than hepatic function in isolation. Muscle wasting is associated with mortality in pretransplant cirrhotic patients, independent of hepatic function [122].

The complications of cirrhosis, including hepatopulmonary syndrome, portopulmonary hypertension, ascites, and peripheral edema, affect exercise tolerance and pulmonary function as well as digestion and metabolism [110]. Cirrhotic cardiomyopathy occurs via impaired beta-adrenergic receptor signaling and alterations in cardiomyocyte membrane lipid composition and ion channels [123] and impairs the ability of the heart to increase cardiac output in response to exercise or other physiologic stress despite a baseline hyperdynamic circulatory system. In the setting of these circulatory changes, patients have an even more difficult time compensating for the anemia that can occur in cirrhosis in relation to malnutrition, alcohol abuse, and variceal hemorrhage. The prescription of beta-blockers for either prevention of variceal bleeding or comorbid cardiovascular indications can further blunt the cardiac response to anemia. Perturbations of pulmonary gas exchange can also decrease exercise capacity in cirrhosis through a variety of mechanisms. Cirrhosis can be associated with comorbid cardiopulmonary disease, basilar atelectasis, and pleural effusions, or hypoxemia can occur due to intrapulmonary shunts in hepatopulmonary syndrome, ventilation-perfusion mismatch, and diffusion-perfusion deficiency [113].

Ability to generate energy from nutrients is essential for exercise tolerance, and the alternations in carbohydrate metabolism described in cirrhosis contribute to impaired exercise capacity [113]. In another metabolic correlate, sarcopenia is common as the hepatic metabolism of glucose and protein changes with ongoing liver damage. Diminished muscle mass as well as a decrease in the ability of skeletal muscles to extract and consume oxygen is seen in cirrhosis [116], and muscle cramps are one of the most bothersome symptoms in patients with cirrhosis [50].

Evaluation of exercise capacity

The majority of research on exercise capacity and strength in liver surgery patients comes from the liver transplant population. These patients are often at the most severe end of the spectrum of liver disease and functional impairment, but consideration should be given to evaluating these parameters in all patients undergoing major hepatectomies. Measurement of VO_2 is ideal and has an independent association with survival

in liver transplant [118, 119]; however, the inexpensive and simple 6-min walk distance test has been shown to be predictive of mortality in patients on the liver transplant waiting list as well [113, 124]. In one study, exercise capacity also demonstrated a significant relationship with duration of posttransplant hospital stay, a finding that should be explored in major hepatectomy patients [118].

There is limited data that handgrip strength correlates with exercise capacity [118] but more research is needed to confirm this association. In one study, handgrip strength was shown to be an independent predictor of complications in patients with cirrhosis [35]. A recent prospective study advocates for the use of a combination of body mass index and thigh muscle thickness measured by ultrasound to diagnose sarcopenia while avoiding costly cross-sectional imaging [125], a technique that would be easy to use preoperatively.

Recommendations for preoperative physical rehabilitation

There are possibilities for preoperative fitness interventions to improve hepatectomy outcomes, and two pilot studies in patients awaiting liver transplantation have demonstrated promising results for exercise training programs. Zenith et al. [126] found that weight weeks of supervised aerobic exercise training in a population of patients with CTP class A and B cirrhosis decreased fatigue while increasing peak VO_2 and muscle mass without adverse effects. Debette-Gratien et al. [127] showed that a personalized 12-week adapted physical activity program in pretransplant patients improved peak VO_2, knee extensor strength, and 6-min walk distance performance while also improving quality of life without complications. Caution must be used in study design and implementation of exercise programs because aerobic exercise has been found to increase hepatic venous pressure gradient, with a 16% pressure increase at 30% of peak workload and 31% pressure increase at 50% of peak workload [128]. This increase can be avoided by premedication with non-selective beta-blockers [129]. In patients with benign hepatic disease and metastatic lesions but otherwise normal liver, this would obviously be less of a concern.

Importance of physical condition in patients with metastatic disease

Physical prehabilitation programs have been studied in cardiac surgery [130], lung resection [131], and bariatric surgery [132] with promising results, but there is limited data on outcomes in patients undergoing surgery for primary or metastatic malignancies. One review of nine studies including five on colorectal cancer, two on bladder cancer, one involving liver resections, and one including abdominal oncological procedures in general found a lack of standardization of programs and outcome measures without significant differences overall in the prehabilitation groups compared to controls [133]. The report on hepatic resection involved a 4-week program of high-intensity cycling sessions, and found improved oxygen uptake and quality of life in the exercise group compared to a control group although compliance with the program, functional capacity, and postoperative complications were not addressed [134].

In a study of colorectal surgery patients who underwent mean 5.4 weeks of prehabilitation with either bike and strengthening exercises or walking and breathing exercises, one third of patients were able to improve their physical function as measured by the 6-min walk distance, and the patients who improved reported improved mental heal and self-perceived health as well [135]. Recognizing the potential impact of these interventions, a large prospective cohort study on cardiopulmonary exercise testing before non-cardiac surgery is currently underway at multiple international locations [136]. While more research is needed, there is potential for a pre-hepatectomy exercise program to improve aerobic capacity and thus mortality, as well as mental health parameters.

Conclusion

Clinical research in nutrition and preoperative preparation has been limited; however, a variety of clinical studies indicate that both patients with primary and metastatic liver disease are vulnerable to nutritional and physical compromise. On the basis of the best available evidence, patients indicated for elective hepatectomy should undergo preoperative nutritional optimization with the use of a short-term high-protein supplement diet. There is also evidence to suggest benefit from an immune supporting blend of amino acids. Selected cirrhotic patients undergoing resection will benefit from intensive postoperative nutritional support, often requiring feeding tube. For patients with steatosis, the optimal preoperative dietary regimen has not been defined; however, it is clear that steatosis is to some degree reversible. These findings lead these authors to routinely utilize 2 to 3 weeks of a calorie-restricted, low-carbohydrate, high-protein diet before surgery. In addition to preventing wound healing and infectious complications and improving patients' quality of life, nutritional and physical optimization during the perioperative period may be associated with improved oncologic outcomes [9, 10]. Even in the modern era, major hepatectomy carries risk of morbidity and mortality, and all patients who are indicated for liver resection should have a thorough evaluation of nutritional and functional status to provide the opportunity to intervene if indicated.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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