Editorial Commentary

The effect of preoperative low-calorie diets on liver resection outcomes

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Introduction

Liver resection is a cornerstone in the treatment of a wide variety of primary and secondary liver pathologies. Despite improvements in operative techniques and surgical technology over the years, the Achilles heel of liver resection remains intraoperative blood loss (1). The latest Cochrane network meta-analysis examining the myriad of perioperative measures (ranging from cardiopulmonary interventions to intraoperative parenchymal transection and hemostatic techniques) aimed at reducing intraoperative blood loss and blood transfusion requirements during liver surgery concluded that low quality evidence was available at best to support a low central venous pressure and the use of certain hemostatic adjuncts (oxidized cellulose and fibrin sealants) (2).

We read with interest the recent randomized controlled trial published by Barth *et al.* examining the role of a short-term preoperative diet in the reduction of intraoperative bleeding during liver resection. It provides a novel and refreshing angle on tackling the problem in juxtaposition with existing literature focused on intraoperative strategies (3). Through a bi-institutional, surgeon-blinded, random permutated block randomized controlled trial (stratified by treatment site) comparing a one-week low-calorie diet (diet group) against a control group (no dietary interventions), Barth *et al.* demonstrated a mean reduction in intraoperative blood loss of 411 mL in the diet group (P=0.02). Other secondary outcomes of interest associated with the dietary intervention reported include a trend towards lower intraoperative blood transfusion requirements (33% *vs.* 53% of patients who required a transfusion, with a mean transfusion volume per patient of 138 *vs.* 322 mL, P=0.06), as well as a significantly improved surgeon-reported ease of liver mobilization and manipulation (average Likert scale score 1.8 *vs.* 2.9, P=0.004).

In light of this study, we set out in this editorial to review (I) the effect of low-calorie diets on physiological changes of the liver; (II) the potential perioperative impact such physiological changes may portend; (III) the clinical application and patient selection in utilizing low-calorie diets as a preoperative intervention; and (IV) directions for further research.

Physiological changes of the liver in response to low-calorie diets

The physiological impact of a low-calorie diet on the liver is two-fold-reduction in liver volume and decreased liver steatosis. These changes have been primarily established in the bariatric surgery and non-alcoholic fatty liver disease (NAFLD) populations respectively (4-6).

While selective liver volumetric modulation through preoperative interventions including portal vein embolization, portal vein ligation and locoregional transarterial therapies (e.g., transarterial chemoembolization, selective internal radiation therapy) have been extensively studied to optimize the future liver remnant following partial liver resections, interventions aimed at decreasing whole liver volume have not been a feature in research surrounding liver resections (7,8). It is however of particular interest in the field of bariatric surgery due to the improvement in visualization and operative manipulation in the upper abdomen with total liver volume reduction. To this end, dietary modification aimed at reducing total caloric intake prior to bariatric surgery has been found to be an effective in preoperative reduction of liver volume by an average of 14% (9). Consequently, the routine use of preoperative dietary modification is encouraged by consensus guidelines in the perioperative management of the bariatric surgery patient so as to improve the technical aspects of surgery (6). Additionally, preoperative dietary modification has also been demonstrated to decrease liver volume in the setting of live liver donors, which in this study, was found to be directly correlated with the decrease in liver steatosis (10).

Liver steatosis is defined as the intracellular accumulation of triglycerides within hepatocytes, which can result from a variety of conditions including alcoholic liver disease, NAFLD, viral hepatitis and drug or toxin-induced (including chemotherapeutic agents) (6). The reduction of liver steatosis, and consequently the risk of progression to steatohepatitis and cirrhosis, is of primary interest in the field of NAFLD, for which lifestyle modifications including diet therapy remains the cornerstone of treatment (6). While a wide array of therapeutic dietary regimes has been proposed, even short-term (less than a week) caloric restriction has been demonstrated to achieve a reduction in liver steatosis prior to significant weight loss (11,12).

Impact on perioperative outcomes

Barth *et al.* postulated one of the primary mechanisms through which their preoperative low-calorie dietary regime contributed to a reduction in intraoperative blood loss during liver resection was via a reduction in liver volume resulting in improvement in liver manipulation (3). While the study did not find a significant reduction in hepatic steatosis with a low-calorie diet (though it was notably not primarily powered to study this), it acknowledged its discordance with existing literature on the aforementioned efficacy of caloric reduction in decreasing liver steatosis. Both intraoperative blood loss and liver steatosis have been found to be independently associated with increased postoperative morbidity and poorer long-term outcomes following liver resection (13-18). The authors postulated that the improvement in liver manipulation was likely due to the loss of hepatocyte glycogen which resulted in the reduction of liver volume. It is also important to emphasize that the authors did not perform actual volumetric measurements of the livers to objectively demonstrate that there was actual reduction in liver volumes resulting in the improvement in liver manipulation.

Intraoperative blood loss and red blood cell transfusion during liver resection has been found to be associated with poorer outcomes (1,13,18). In the short-term, postoperative morbidity and mortality rates have been reported to be increased, in part attributable to the immunomodulatory effects blood transfusion has on the recipient (1,13,18). In the longer-term following liver resection for neoplastic indications, there have been reported associations with decreased disease-specific and overall survival (1,18).

Liver steatosis (and steatohepatitis) in particular has been examined extensively in the context of liver resection for colorectal liver metastases, which has been reported as a predictor of increased morbidity (including posthepatectomy liver failure rates) and poorer overall and disease-free survival rates (13-17). This may in part be explained by the deleterious effects steatosis has on liver microcirculation, tolerance against ischemic injury and regenerative abilities following major parenchymal loss (19). Steatosis is of further clinical significance in the setting of liver metastasectomy which often occurs in the setting of multimodality treatment including systemic chemotherapy, which has been found to induce steatosis and steatohepatitis, with consequent impact on post-liver resection morbidity rates (20).

Clinical application and patient selection

In light of the established detrimental effects intraoperative blood loss and liver steatosis have following liver resection, and the potential for amelioration of these poor prognosticators in part by preoperative low-calorie dietary interventions, how may surgeons best employ this in clinical practice? Optimal patient and case selection for preoperative low-calorie dietary interventions should seek to maximize potential benefits (in terms of reducing intraoperative blood loss and liver steatosis) whilst minimizing any possible adverse effects of such a dietary regime.

Patients who may reap the greatest benefits from a low-calorie preoperative diet are likely those who mirror the patient populations in which these beneficial physiological liver alterations have been established—obese patients with steatotic livers, without significant underlying hepatic insufficiency (5,6). In retrospect, a possible reason accounting for the lack of reduction in liver steatosis associated with a low-calorie preoperative diet in the trial by Barth *et al.* could be a relatively low (in comparison to bariatric populations) baseline body mass index (BMI), without any indication of the baseline prevalence of liver steatosis within the study population (3). As such, a baseline assessment of nutritional status and liver steatosis would be prudent prior to employing low-calorie preoperative diets.

Anthropometric parameters such as the BMI have been found to correlate with the prevalence of liver steatosis, with NAFLD rates of 65% and 85% of patients with BMI 30.0–39.9 and ≥40.0 respectively (21). A caveat to consider however in the setting of liver surgery is the confounding effect of ascites on BMI in patients with chronic liver disease who may be correspondingly under-nourished for a given BMI range. Such patients with pre-existing hepatic insufficiency may also tolerate a low-calorie diet poorly due to diminished hepatic glycogen reserves and impaired glucose homeostasis, and may be more susceptible to adverse effects from such preoperative dietary interventions.

Radiological modalities such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) are useful adjuncts in the non-invasive assessment of underlying liver steatosis (21,22). MRI in particular (specifically MR proton-density fat fraction and MR spectroscopy) has emerged as the non-invasive assessment method of choice, which has been widely used in clinical and trial settings when examining changes in liver steatosis in response to therapeutic interventions (22). Assessment of liver steatosis on liver biopsies—the gold standard—can be reserved for patients who have other indications for preoperative liver biopsy (e.g., confirmation of liver metastasis) who may subsequently undergo liver resection.

Taken together, non-malnourished patients with liver steatosis and without significant underlying hepatic insufficiency are theoretically most likely to benefit from a low-calorie diet prior to liver resection. Such patients, as correspondingly reflected in the recruited patient population in the study by Barth *et al.* which only included patients with a BMI more than 25, would include those undergoing liver resection for liver metastasis (most commonly for colorectal liver metastases), gallbladder cancer and intrahepatic cholangiocarcinoma (3).

Future directions

Further studies are required to affirm the reproducibility of a reduction in intraoperative blood loss during liver resections with a low-calorie preoperative diet, better examine the physiological effect of such a diet on liver steatosis, and characterize patient subgroups who may best benefit from such an intervention. Concomitant investigations should also focus on incremental therapeutic effects with dietary regime modification (e.g., lowering daily caloric intake, extending duration of preoperative dietary intervention) weighed against possible plateauing of desired outcomes and increased rates of adverse effects. To parallel investigational therapies in the treatment of NAFLD, studies can also examine preoperative dietary modifications beyond caloric restriction. For instance, *in vivo* studies on a mouse hepatectomy model by Linecker *et al.* reported reversal of liver steatosis and improved liver regeneration associated with the preoperative administration of omega-3 fatty acids (23). Given the relatively low rates of adverse events expected with a low-calorie dietary intervention, the safety profile can be better determined from eventual large cohort studies, which will also provide longer term follow-up data to elucidate the impact on long-term outcomes such as local disease recurrence and survival. In future studies, it would also be interesting to determine the actual reduction in liver volumes and their correlation with patient BMI and determine patients' actual weight loss with the low-calorie diet.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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