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Influence of nutritional status in the postoperative period of patients with inflammatory bowel disease

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Abstract

Inflammatory bowel diseases (IBDs) are a group of chronic inflammatory diseases that affect the gastrointestinal tract, including Crohn's disease (CD) and ulcerative colitis. Surgery is a treatment option, and more than half of the patients with CD will undergo surgical interventions over the course of the disease. Postoperative complications are common in IBD patients, the most frequent being intra-abdominal sepsis, infection of the surgical site, and adynamic ileum, and nutritional status is a factor that can influence postoperative outcome. Recent studies have shown that malnutrition, obesity, sarcopenia, and myosteotosis are predictors of surgical complications. However, most were retrospective studies with small patient samples and heterogeneity of clinical and nutritional assessment methods, which limit the extrapolation of data. Therefore, knowing the pathophysiological mechanisms of IBD and identifying the best parameters for assessing nutritional status are essential for prompt implementation of adequate nutritional interventions.

Key Words: Inflammatory bowel diseases; Crohn disease; Ulcerative colitis; Nutritional status; Postoperative complications; Surgery

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Core Tip: Nutritional status influences the postsurgical results of patients with inflammatory bowel diseases (IBDs). Despite the limitations of previously published studies, malnutrition, obesity, sarcopenia, and myosteotosis were identified as negative predictive factors for postoperative complications in people diagnosed with IBDs.

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INTRODUCTION

Inflammatory bowel diseases (IBDs) are a group of chronic inflammatory diseases that affect the gastrointestinal tract, and the most common are Crohn's disease (CD) and ulcerative colitis (UC)[1]. Although the incidence of IBD in most Western countries is stable, the prevalence exceeds 0.3% in some regions, which results in a high disease burden[2]. In addition to drug therapy, surgical interventions are needed by most patients with CD[3]. In IBD, surgery is indicated for clinical intractability, complications, and neoplasms, and is considered an option in CD patients with isolated ileal disease[4]. Postoperative complications are frequent in IBD, especially intra-abdominal sepsis, surgical site infection (SSI), and adynamic ileum[5-9]. Increased understanding of the effects of nutritional status on surgical outcomes and the patient characteristics that are predictive of surgery-associated complications are essential for prompt implementation of adequate nutritional interventions[10]. The purpose of this review was to gather scientific evidence on the influence of nutritional status in the postoperative period of people with IBD.

IBDs

Although the details are not completely clear, it is assumed that the pathogenesis of IBD involves genetic, environmental, and immunological factors[1]. The clinical course of the disease is highly variable but is most often characterized by periods of activity and remission[11]. The last 100 years have seen an increase and stabilization in the occurrence of IBD in Western countries, while in some countries in Africa, Asia, and South America, the incidence continues to increase and still lacks stability. This trend has been attributed mainly to Westernization and recent industrialization in those regions. Given the reality and economic impact of IBD, healthcare systems and professionals must be prepared to implement prevention policies, conduct scientific research, and provide adequate attention to the IBD population[12,13]. Currently, the therapeutic objectives of IBD include symptomatic treatment, induction of clinical remission, and other goals, such as the prevention of complications, healing of the mucosa, improvement of quality of life, and remission without the need of steroids[14, 15]. In addition to medications (*e.g.*, aminosalicylates, corticosteroids, immunomodulators, and immunobiologics) and enteral nutritional therapy exclusively for the pediatric population, surgical procedures can also be used to treat IBD patients[16,17].

SURGICAL TREATMENT

Elective surgery may be indicated for UC and CD patients[18]. IBD patients presenting with toxic colitis, bleeding, perforations, obstructions, and abscesses usually require emergency surgical interventions[19]. Chronic intestinal inflammation and prolonged treatment with immunosuppressive drugs increase the risk of the development of gastrointestinal neoplasms in IBD patients[20]. The presence of IBD in patients with colorectal cancer increases the risk of prolonged hospitalization following surgery, hospital readmission within 30 d of discharge, open surgery, total colectomy, total proctocolectomy, deep vein thrombosis, and postoperative infection[21].

Most people diagnosed with CD will need surgery, and approximately half will have a recurrence after intestinal resection. The presence of disease in any region of the small intestine, perianal fistula, and an age between 45 and 59 years increase the relative risk of surgery[3]. The main objectives of surgical treatment are symptom control, maintenance of intestinal function, and anatomical preservation of organs[18]. Studies have shown that the percentage of postoperative complications varies from 9% to 33%, with intra-abdominal sepsis following an anastomotic leak, intra-abdominal collection, or a parietal abscess; SSI, and adynamic ileum (*i.e.* the absence of bowel

muscle contraction movements)[22,23].

Patients with CD undergoing ileal resection often experience malabsorption of bile acids. Bile acids are essential for the digestion of fats, and their active reabsorption occurs in the distal ileum. The absence of this portion of the intestine compromises the digestion of lipids in the diet, promoting steatorrhea, fecal excretion of fats. In addition, ileal resection and the consequent accumulation of bile acids in the lumen can increase intestinal permeability and motility, impair the integrity of the mucosa, promote bacterial overgrowth, and favor the formation of kidney and gallstones. The selenium homotaurocholic acid test is the gold standard method for detecting the condition, and the first line of treatment is the use of intraluminal bile acid ligands such as cholestyramine[24-27]. Surgery is performed less often in patients with UC and may be indicated in cases of neoplasia, dysplasia, and refractory disease. The most common interventions include total proctocolectomy with permanent terminal ileostomy and the making of an ileal pouch with anastomosis to the anal canal. Among the main risk factors for both early colectomy and late colectomy are male sex and hospitalization at diagnosis[18,28]. The occurrence of postoperative complications in UC varied from 9% to 65% (early) and from 17% to 55% (late), and was higher than the occurrence of complications in CD. Adynamic ileum, infection, and pouchitis were the most common complications observed in the UC population[29,30]. Compared with open surgery, laparoscopy is a minimally invasive technique with better 30 d postoperative outcomes, especially in relation to the need for a pulmonary ventilator after 48 h, organ space infection, superficial and deep SSI, urinary tract infection, and renal failure[31]. It should be noted that regardless of the type of surgery, the surgeon's primary goal is to ensure performance of a long-lasting, reproducible, and safe procedure[32].

Although the literature is controversial, a systematic review and meta-analysis found that the use of corticosteroids and anti-tumor necrosis factor increased the risk of intra-abdominal infections in the postoperative period[33]. In addition, in the era of biological products, it has been observed that after non-elective surgery, mortality has remained high in UC and has slightly decreased in CD. A population-based study found that mortality was primarily associated with comorbidities and age[34,35].

NUTRITIONAL STATUS AND POSTOPERATIVE COMPLICATIONS

Surgery is an invasive procedure that results in tissue damage, the breaking of a physical barrier, and possible exposure to microorganisms that result in inflammation and metabolic stress. Inflammation involves innate and adaptive immune responses and pro- and anti-inflammatory mediators. The severity of the inflammatory response depends, among other factors, on age and the type and location of the surgery, the medications used, and preoperative health status[36].

Malnutrition

In patients with IBD, malnutrition often prolongs the inflammatory response and slows recovery from illness and surgery, hinders wound healing, and is related to increased hospital stay and healthcare costs[37-39]. Various factors contribute to the deterioration of nutritional status in this population, such as reduced food intake, increased intestinal losses, malabsorption of nutrients, increased nutritional needs associated with systemic inflammation, and iatrogenic factors (*e.g.*, surgery and medications)[40,41]. As malnutrition is a modifiable risk factor for adverse outcomes of surgery, prompt identification enables early nutritional interventions[10], several studies have investigated methods of preoperative nutritional assessment[42-45].

Body mass index (BMI) is a practical, widely used predictor of surgical complications. A low BMI seems to increase the risk of postoperative infectious complications and intra-abdominal sepsis in patients with CD, and is better predictor than serum albumin concentration[46,47]. However, recent studies have identified preoperative hypoalbuminemia is a risk factor for complications in both CD and UC, and that the incidence of undesirable outcomes was increased in eutrophic patients with hypoalbuminemia[45,48]. It is noteworthy that the studies were retrospective and had small patient samples, therefore, the results should be interpreted with caution[46,47]. In fact, serum albumin may not be a good marker of the nutritional status of patients with IBD, especially in the active phase[49].

Both albumin and C-reactive protein (CRP) are acute-phase proteins, and their concentrations change with the inflammation that occurs after surgical trauma[50]. The CRP/albumin ratio (CAR) is considered as a novel prognostic index based on inflam-

mation. A study including IBD patients undergoing elective colorectal surgery found that postoperative CAR predicted surgical complications, more accurately than CRP alone. Patients with a CAR ≥ 2.2 had increased risks of complications, prolonged hospital stays, and SSIs, which indicated that value was of possible use as a cutoff for the early detection of undesirable results[51]. The CAR was also able to predict postsurgical survival in people with colorectal cancer[52].

Considering the limitations of nutritional status markers, the preoperative assessment must be complete, including the assessment of nutritional risk scores and information about food consumption and weight loss[53]. The guidelines of the European Society for Clinical Nutrition and Metabolism on nutrition in surgery define severe nutritional risk as the presence of least one of the following: Weight loss $> 10\%$ - 15% in 6 mo; a BMI < 18.5 kg/m²; Subjective Global Assessment grade C or Nutritional Risk Screening > 5 ; or a preoperative serum albumin < 30 g/L without evidence of hepatic or renal dysfunction[38].

Obesity

The prevalence of overweight and obesity has increased in both the general population and in people with IBD[54-56]. Obesity is an inflammatory state, and the metabolic activity of adipose tissue includes the secretion of pro- and anti-inflammatory cytokines that can promote immune-mediated diseases such as IBD[57]. Data on the influence of obesity on IBD are controversial. Some studies show an association with unfavorable outcomes of the disease, such as the need for surgery and hospitalization, reduced drug efficacy, and complications[57-59]. Others have not demonstrated such associations[60-63] and consider obesity to be a marker of less severe disease[62].

It has been suggested that obesity has a negative influence on postoperative results [57]. Despite having less disease severity at the time of surgery, obesity increased the risk of SSI in CD patients after ileocolic resection, as well as the risk of requiring laparoscopic modification of conventional surgery, which may lead to worse outcomes in the future[31,64]. A recent meta-analysis concluded that obesity was associated with general postsurgical complications, high SSI rates, greater blood loss, and longer hospital stays in patients with IBD[65]. A point to be highlighted is that SSI is related to the size of the surgical extraction site, which tends to be larger in obese patients[64]. Because SSI is likely to prolong hospitalization and has been shown to increase readmission rates after colectomy, preoperative weight loss has been suggested in order to minimize it[66,67].

Few studies have investigated the effect of weight loss on the outcomes following surgery for IBD[57]. Bariatric surgery is one of the ways of treating obesity[68], but its use in IBD is limited because of the complexity of those diseases and the scarcity of studies to support the decision-making of health professionals[69]. Reviews of the impact of bariatric surgery on the clinical course of IBD found that it is relatively safe and reduces the risk of complications[69,70]; however, more robust original articles evaluating surgical outcomes must be added to the literature to increase the reliability of those findings. It should be noted that malnutrition is common in patients with IBD and that people with high BMIs may also have nutritional deficiencies[37,71,72]. Therefore, it is essential to carry out a thorough nutritional assessment of possible candidates for bariatric surgery[69].

Most studies use BMI to determine obesity. However, the index has limitations, such as the inability to distinguish body composition and fat distribution. Although interest in the role of visceral fat in IBD patients has increased recently, few clinical trials have been conducted. The available results include associations between body fat measurements (mesenteric fat index, morphometric analysis, visceral fat area) and inflammation and postsurgical complications that were not observed when BMI was chosen as a variable[73-75].

Sarcopenia

In IBD patients, malnutrition and excess weight can coexist with sarcopenia, which is a skeletal muscle syndrome characterized by progressive and generalized reduction in the quantity and quality (*i.e.* strength or physical performance) of muscle mass[76]. The etiology of sarcopenia is multifactorial, involving aging, physical inactivity, presence of other diseases (*e.g.*, inflammatory, malignant and endocrine), organ failure, and inadequate intake or use of nutrients (*e.g.*, anorexia, malabsorption, limited access to healthy foods and drug interactions). In the last 10 years, several studies conducted in different populations reported that muscle strength has a prominent role[77,78].

In a meta-analysis, sarcopenia was found to be an independent risk factor for the need of surgery and the occurrence of postoperative complications, with no difference between UC and CD. However, the data should not be extrapolated, as all the studies

evaluated sarcopenia only by body composition and the muscle mass; type of surgery and postsurgical outcome data were heterogeneous[79]. In a study that evaluated only people with CD, Galata *et al*[80] observed that the skeletal muscle mass index was the only risk factor for abscesses and anastomotic leaks. Patients with sarcopenia had lower serum albumin levels and BMIs and higher CRP levels, which can be useful indicators for nutritional screening of the syndrome[79].

Although it is more common in malnourished people, sarcopenia can affect those who are overweight. A study carried out in 90 IBD patients with sarcopenia defined as a low skeletal muscle mass in a computed tomography cross-section at the L3 vertebral level, found that a BMI ≥ 25 kg/m² predicted the need for surgery. However, the sample number was limited ($n = 3$) and there was no information on the surgical results[81].

Myosteatorsis

Myosteatorsis is a negative prognostic factor in cancer and has been associated with worse overall survival in a variety of cancers[82,83]. The pathophysiology of myosteatorsis is not well understood, but it is believed that there is a relationship between aging and excess weight that results in ectopic fat deposition in skeletal muscle[84]. O'Brien *et al*[85] found that the hospital stays were longer and readmissions 30 d after bowel resection were more frequent in IBD patients with myosteatorsis. There are few recent studies of the effects of the change in body composition that occurs in myosteatorsis. Better knowledge of the pathogenesis and validation of diagnostic criteria for myosteatorsis are essential for conducting reliable studies to elucidate the impact of this condition on postoperative evolution and to accurately assess preoperative nutritional status[83].

Nutritional support

Insufficient food intake increases the risk of postoperative complications of abdominal surgery. The optimization of nutritional status in the preoperative period contributes to better surgical results in CD patients[86,87]. Given the importance of perioperative nutritional support, new IBD guidelines recommend early initiation of nutritional therapy in patients with malnutrition and/or unsatisfactory food consumption. The recommendation stems from a prediction of the inability to eat for more than 7 d in the perioperative period and impossibility of maintaining an oral intake above 60%-75% of nutritional needs for more than 10 d[27].

The choice of the type of nutritional therapy will depend on the clinical condition and nutritional status of the patient. Whenever possible, one should choose enteral nutrition (EN) over parenteral nutrition (PN). However, if EN does not supply more than 60% of the energy needs, then EN should be supplemented by PN, especially in the perioperative period. Exclusive PN is indicated in patients with diarrhea and severe vomiting, absence of access, bowel obstruction, severe shock, intestinal ischemia, high output fistula, and severe intestinal bleeding[27,53].

Most of the guidelines contained in the Enhanced Recovery After Surgery protocols can be applied to IBD patients undergoing surgical interventions. From a metabolic and nutritional perspective, some precautions must be taken in order to speed up postoperative recovery and reduce hospital stay. They include avoiding long periods of fasting before surgery, promoting metabolic and blood glucose control, reducing factors that intensify catabolism or impair the function of the gastrointestinal tract, re-establishing oral feeding as soon as possible, and promoting early mobilization in order to favor protein synthesis[27,38,53].

CONCLUSION

Surgical intervention during the course of IBD is a common practice, and postsurgical complications such as intra-abdominal sepsis, SSI, and adynamic ileum are prevalent. Nutritional status that involves malnutrition, obesity, sarcopenia, and myosteatorsis is predictive of the worst outcomes of surgery by increasing the risk infectious and noninfectious complications. Further studies are needed to understand the pathophysiological mechanisms, standardize diagnostic criteria and determine the best preoperative nutritional assessments. This knowledge is essential to establish measures to prevent postsurgical complication in IBD patients.

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Overview on drug-induced liver injury in Brazil

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Abstract

Drug-induced liver injury (DILI) is an uncommon event in clinical practice, which makes knowing its true incidence difficult. Prospective, retrospective and registry-based studies are the most important methods to obtain epidemiological data on DILI. Latin America (LA) has a historical lack of prospective studies on this topic. New definitions and the creation of hepatotoxicity registries have significantly improved the epidemiological understanding of hepatic drug reactions in several regions of the world. The Latin American DILI network, referred to as LATINDILI, has been created in 2011, and recently published its own DILI recommendations describing the most relevant issues on the management of hepatotoxicity in general, and those based on findings from our own LA experience in particular. Although most of the registries do not carry out population-based studies, they may provide important data related to the prevalence of DILI. The joint work among researchers and the corresponding health and regulatory authorities should be stimulated due to the high impact that hepatotoxicity represents for public health.

Key Words: Hepatotoxicity; Drug-induced liver injury; Drug-induced liver injury registries; Herbs; Hepatitis

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Core Tip: Liver damage induced by drugs and herbs was historically underreported in Latin America until the advent of a Latin American Registry of Hepatotoxicity (LATINDILI), which progressively improved knowledge about the most frequently involved drugs inducing liver injury in this region. This article letter emphasizes on the value of being able to centralize cases linked to hepatotoxicity in a Latin American drug-induced liver injury network, and discuss the present and future advantages of this

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valuable tool, which should work along with regulatory entities to achieve a high impact on public health policy.

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TO THE EDITOR

I have read with great interest the systematic review by Becker *et al*[1], analyzing Drug-induced liver injury (DILI) publications in Brazil. The authors carried out a thorough search on the main bibliographic sources over a long period of time, including several decades.

Our group published more than a decade ago a review on DILI articles reported from Latin America (LA) up to 2010[2]. Only well documented case reports and series with a small number of patients could be identified. We found the same difficulties to Becker *et al*[1], since the definitions used for DILI were heterogeneous at that moment, and we did not find any prospective or retrospective studies carried out with a careful and detailed design that would have involved a large number of patients[2].

Many papers published before 2011 do not meet the criteria for DILI proposed by an expert meeting led by Aithal *et al*[3], which defined hepatotoxicity as (1) An ALT elevation ≥ 5 upper limit of normal (ULN), (2) An ALP elevation ≥ 2 ULN, or (3) An ALT elevation ≥ 3 ULN with a simultaneous elevation of total bilirubin concentration ≥ 2 ULN[3].

Of note, liver enzymes elevation below this cutoff are nowadays interpreted as adaptive phenomena. This is a very frequent asymptomatic biochemical issue observed at the beginning of drug intake, and it should not be initially interpreted as hepatotoxicity, because these biochemical parameters usually return to normal values despite continued drug consumption[4].

All DILI articles coming from LA should mention our LATINDILI registry, because, for the first time, we have a very well-structured hepatotoxicity network capable of recruiting patients associated with liver damage induced by drugs, thus being able to study the epidemiological behavior of medicaments and herbs used more often in our region[2]. This ambitious research project became a registry in 2011, and has already recruited more than 400 patients, with 8% of them corresponding to herbal-induced liver toxicity (HILI). Unfortunately, our registry was not mentioned by Becker *et al*[1]. However, its recognition would have helped them to establish better reference points for comparisons within the region and guidance on DILI distinction based on our operational criterion[2].

LATINDILI is a collaborative and interdisciplinary network aimed to (1) Establish the characteristics of DILI expression, search for risk factors, and evaluate the outcome; (2) Improve the instruments for causality assessment; (3) Increase knowledge on etiopathogenic mechanisms and identification of susceptible subjects; and (4) Help to develop diagnostic and predictive biomarkers in DILI[2].

Interestingly, the authors also stated that their research is expected to broaden the debate to establish a solid pharmacovigilance policy and the creation of a wide national DILI monitoring network and its integration with other DILI networks[1]. This is a very important point linked to one of the main objectives of DILI registries, which highlight the importance of working in close connection with regulatory and health authorities to strengthen both pharmacovigilance and the reporting cases of drug-induced liver reactions[5].

In addition, one of the most relevant objectives from our registry is to make physicians fully aware that hepatotoxicity is a distinct disease in which we have to improve its early diagnosis and management, and to be able to report these cases to the LATINDILI registry. If this feedback works in a regular and organized manner, it will allow clinicians to design and facilitate the carry out of multicenter clinical trials to assess the effect of new therapeutic agents with potential to induce idiosyncratic DILI [6].

Finally, LA already has its recommendation position paper for DILI management, which include our own data, and reinforces points exclusively inherent to LA, such as the differential diagnoses that should be made regarding the presence of tropical diseases, which can be mistakenly interpreted as DILI.

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