Inflammatory Bowel Diseases, 2023, **XX**, 1–4
https://doi.org/10.1093/ibd/izad235
Advance access publication 20 October 2023
Invited Editorial

Get Fit: Muscle Health for Crohn's Disease Surgical Outcome Optimization

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Lay Summary

Muscular health, encompassing sarcopenia and myosteatosis, has a pivotal role in optimizing surgical outcomes in patients with Crohn's disease. A comprehensive approach is advocated for improving patient well-being after surgery.

Key Words: inflammatory bowel disease, IBD, sarcopenia, myosteatosis, muscular health, Crohn's disease surgery

Crohn's disease (CD) is a chronic inflammatory bowel disease characterized by several clinical challenges that extend beyond just intestinal symptoms. CD can significantly affect patients' quality of life and often requires surgical intervention. Indeed, approximately 25% of patients with CD require major abdominal surgery within 10 years of diagnosis.[1,2]

CD requires comprehensive strategies to improve surgical outcomes. The need to prevent and limit surgical complications and improve surgical outcomes has sparked the exploration of innovative strategies that extend beyond the traditional boundaries of surgery. The interplay between chronic inflammation in CD and its systemic consequences underscores the need to address extraintestinal manifestations as well. Among these, the impact on skeletal muscle health is becoming increasingly evident, and one such emerging paradigm involves recognizing the crucial role of sarcopenia on the outcomes of CD surgery.[3,4]

In the current issue of *Inflammatory Bowel Diseases*, Donnelly et al[5] presents the results of their study providing valuable insight into these factors and their implications. Not only sarcopenia, but also markers of myosteatosis, including intramuscular adipose tissue and muscle attenuation, were significantly associated with increased complications. In contrast, measures of adiposity, such as total fat area and visceral fat area, did not exhibit a significant association with overall morbidity. This underscores the primary critical role of muscular health in determining patient outcomes in CD surgery, rather than solely the presence of obesity. Indeed, in the same study, a substantial proportion of patients exhibited obesity, with approximately one-quarter exhibiting visceral obesity. Interestingly, larger fat stores were associated with a lower risk of emergency admission but correlated with increased corticosteroid use. This paradoxical relationship suggests a potential protective effect of fat stores against specific disease complications and the deleterious effects of malnutrition on inflammation and vice versa. However, visceral fat area independently predicted an increased risk of venous thromboembolism, whereas total fat area was associated with an increased risk of wound infection.

These findings underscore the need for a comprehensive assessment of the patient's nutritional status and muscle composition before surgery to optimize outcomes. Therefore, recognition of the role of muscle in CD patients undergoing surgery is paramount.

Sarcopenia, characterized by progressive loss of muscle mass and strength, and myosteatosis, the infiltration of muscles with fat, are intricate manifestations that are often exacerbated by CD-associated factors (**Table 1**).[3,6,7] A deeper understanding of the biochemical mechanisms underlying muscle health in CD is crucial. Chronic inflammation, a hallmark of CD, triggers the release of proinflammatory cytokines, notably interleukin-6 and tumor necrosis factor α. These cytokines initiate a cascade of events, including the activation of the ubiquitin-proteasome system, leading to muscle protein degradation, exerting a potent catabolic effect on skeletal muscle,[8] and exacerbating sarcopenia. Additionally, oxidative stress, induced by the overproduction of reactive oxygen species, damages mitochondria and impairs energy production and muscle function.[9] This phenomenon is not only a byproduct of the disease itself but is often exacerbated by long-term medication use, decreased physical activity, and impaired nutritional status.[3] As a result, CD patients often face a double burden—the inherent challenges of the disease and the secondary consequences that affect their muscle health.

Received for publication: September 15, 2023. Editorial Decision: September 17, 2023

Table 1. Potential causes of sarcopenia in CD, encompassing factors related to inflammation, oxidative stress, medication use, nutrition, and indirect consequences of CD.

1. Chronic inflammation	Release of proinflammatory cytokines (eg, IL-6, TNF-α)
	Activation of the ubiquitin-proteasome system leading to muscle protein degradation
	Exacerbation of muscle wasting and catabolic effects on skeletal muscle
	Interplay of cytokines with anabolic resistance affects muscle protein synthesis
2. Oxidative stress	Overproduction of reactive oxygen species
	Damage to mitochondria, impairing energy production and muscle function
3. Long-Term Medication Use	Medications used for CD management can contribute to muscle loss, because of side effects or drug-related fatigue that can further discourage physical activity
	Intravenous administration of certain drugs can imply hospitalization and reduced physical activity
4. Impaired nutritional status (either hyponutrition or hypernutrition)	Malnutrition, including sarcopenic obesity, compromises muscle health
5. Indirect consequences of CD	Reduced physical activity due to disease symptoms, especially fatigue or pain that limits the patient's ability to exercise
	Impaired nutritional intake due to gastrointestinal symptoms

Abbreviations: CD, Crohn's disease; IL, interleukin; TNF-α, tumor necrosis factor α.

Conversely, any form of malnutrition, including sarcopenic obesity, implies a chronic inflammatory state that may exacerbate the clinical course of chronic inflammatory disease.[7,10,11] Recently, the impact of malnutrition in all its facets, including malnutrition and sarcopenia as well as obesity, sarcopenic obesity, and myosteatosis, on clinical outcomes in CD surgery has garnered attention.[6,7,10,11] Optimizing patients for surgical procedures has traditionally focused on factors such as nutritional status, comorbidities, and preoperative screening for frailty.[12] However, there is growing evidence that impaired muscle mass and function are related to surgical outcomes in CD patients.[3,4,13] Skeletal muscle plays a critical role in the recovery process, and sarcopenia has been found to be associated with worsened baseline nutritional markers, suggesting a close relationship between muscle mass and nutritional status. Decreased muscle mass has been associated with delayed wound healing,[14] increased risk of infection,[15] longer hospital stays, and increased morbidity.[16,17]

Moving forward, these findings should stimulate further research aimed at exploring interventions that target muscle mass and function to enhance outcomes of CD surgery, and emerging care paradigms need to incorporate muscle health into prehabilitation programs,[18] even in the context of CD surgery. By exploring the intricate mechanisms by which inflammation, oxidative stress, and anabolic resistance interact, clinicians and researchers have the opportunity to explore innovative strategies that could potentially revolutionize the care of CD patients toward personalized and holistic optimization strategies. Indeed, optimizing muscle health is becoming increasingly important.[19]

Insights into the biochemical relationship between inflammation, oxidative stress, and muscle catabolism represent the basis for tailored interventions targeting these mechanisms. Physical exercise, particularly resistance training, is emerging as a cornerstone to counteract muscle wasting and anabolic resistance.[20] Indeed, physical therapy and exercise programs, even in a preoperative setting tailored to the patient's condition, can help maintain and even increase muscle mass. Exercise, for example, has the potential to counteract muscle wasting by stimulating muscle protein synthesis. In particular, resistance training activates the mTORC1 pathway, promoting muscle protein synthesis and counteracting the anabolic resistance observed in CD patients.

In addition, individualized nutritional strategies that also target anabolic resistance and attenuate oxidative stress further increase the potential for better surgical outcomes.[19,21] While limited evidence exists regarding the benefits of higher intakes of specific nutrients for addressing sarcopenia, the data supporting the impact of "healthier" diets of higher quality are compelling. Strategic nutritional interventions, rich in essential amino acids, may supply the necessary substrates for muscle protein synthesis while concurrently mitigating oxidative stress through antioxidants. This approach holds promise for reversing the catabolic effects of the disease and promoting muscle growth. Nevertheless, clinical trials are imperative to conduct further investigations into these dietary effects.

Strategies aimed at maintaining or enhancing muscle health, along with optimized nutrition, offer a multifaceted approach for patients with CD and may help mitigate postoperative complications and facilitate recovery.

Given the increasing recognition of the importance of nutrition and muscle health, it would also be useful to design clinical trials that examine not only the effect of exercise programs targeting sarcopenia, but also different types of training (eg, resistance, endurance, etc.) in combination with different nutritional strategies (eg, high-protein diets, diets enriched with essential amino acids). These studies should be rigorous and have the same scientific integrity as pharmacological interventions. This is especially possible because patients undergoing surgery for CD are relatively young, making them an ideal population for conducting these interventions. Such studies would provide valuable insight into the most effective approaches to optimize muscle health in patients with CD and ultimately contribute to better surgical outcomes. In addition, exploring the indirect pharmacological effects of drugs targeting proinflammatory cytokines, oxidative stress, and anabolic resistance pathways is a promising area.

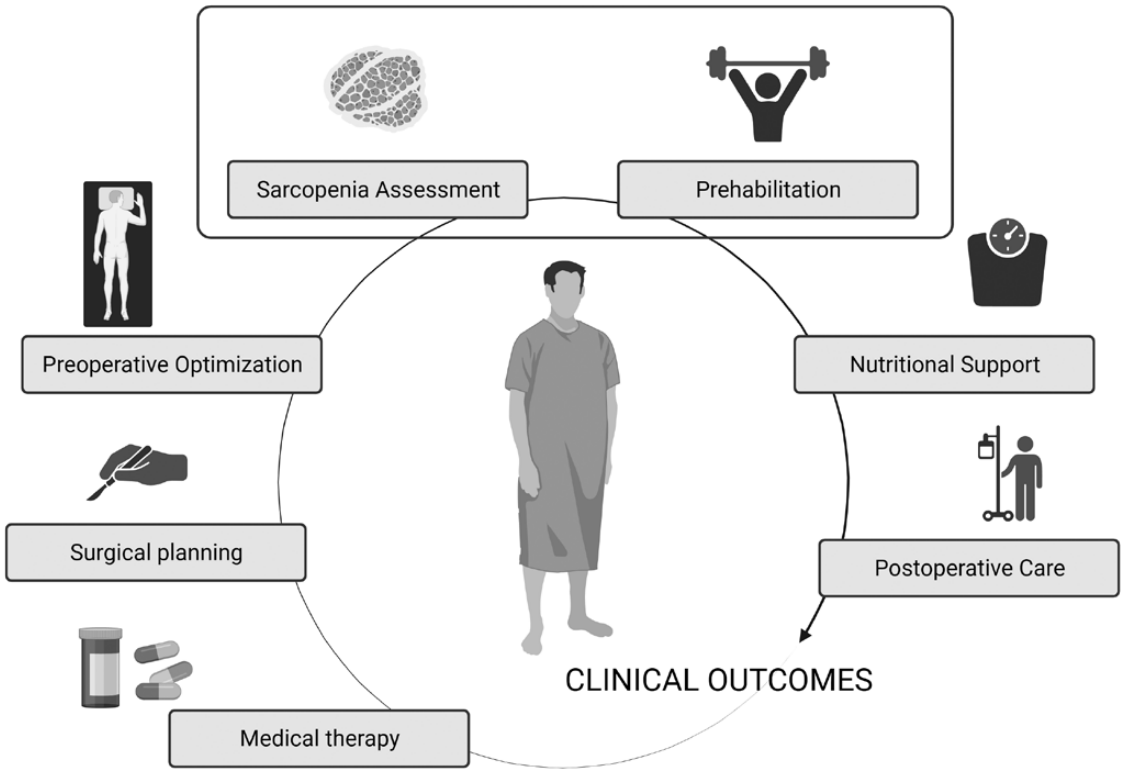

Figure 1. Holistic approach of Crohn's disease surgery. Comprehensive assessment combining biological insights and medical and surgical interventions is essential in Crohn's disease surgery to achieve better outcomes.

The intricate biochemical interplay between chronic inflammation, muscle wasting, and functional impairment in CD patients lends itself to precision medicine approaches. These approaches toward improved surgical outcomes for patients with CD require collaboration between multiple specialists. Surgeons, gastroenterologists, nutritionists, and physical therapists need to work hand-in-hand to develop comprehensive care plans that not only address the disease, but also focus on the patient's overall health, including their muscle health.

Therefore, precision medicine is reshaping CD surgery to achieve better outcomes by combining biological insights, and medical and surgical interventions, resulting in optimized postoperative recovery and improved quality of life (Figure 1). This holistic approach highlights the importance of this integration and introduces an era defined by refined efficacy and personalized interventions. Through such an integrative approach, surgical outcomes for patients with CD have the potential for significant improvement, redefining the therapeutic landscape.

Author Contribution

S.M. and S.D. conceived and planned the article. S.M. conducted the literature search and P.S. assisted in writing the first draft of the manuscript. S.M. took the lead in writing and revising the manuscript. All authors provided critical feedback and contributed to shaping the content. S.D. reviewed the manuscript for important intellectual content and prepared the final version of the article. All authors have reviewed and approved the final version of the manuscript. S.D. is the guarantor of the article.

Funding

This paper received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

S.D. has received consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Enthera, Ferring Pharmaceuticals Inc, Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB Inc, and Vifor. The other authors have no disclosures.

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