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Review

Nutritional Challenges and Management in Patients with Inflammatory Bowel Diseases: A Comprehensive Review

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Abstract

Nutritional management in inflammatory bowel diseases (IBD) is transitioning from a calorie-centric approach to a functional paradigm that incorporates body composition, metabolic health, and inflammatory burden. Malnutrition, which may manifest as sarcopenia, myosteatosis, or sarcopenic obesity, affects a significant proportion of patients from the time of diagnosis and has prognostic implications for treatment response, surgical outcomes, and quality of life that go beyond those associated with Body Mass Index (BMI) alone. This narrative review explores the evolving role of nutrition as both a disease modifier and a therapeutic adjunct in IBD, emphasizing mechanistic evidence that links ultra-processed foods and dietary additives to intestinal barrier disruption, dysbiosis, and persistent low-grade inflammation. We propose a phase-specific framework that positions nutritional assessment and dietary intervention as essential components of routine IBD care. During active disease, targeted exclusion diets can function as therapeutic adjuncts or, in selected cases, as primary interventions. During remission, adherence to anti-inflammatory dietary patterns, particularly the Mediterranean diet, promotes microbiota diversity, mucosal integrity, and long-term metabolic resilience. Nutritional interventions should be coordinated with pharmacological therapy to capitalize on the therapeutic window created by inflammatory suppression, thereby overcoming anabolic resistance and optimizing muscle protein synthesis. Standardized screening tools that integrate the Global Leadership Initiative on Malnutrition (GLIM) criteria with body composition analysis facilitate early identification of nutritional phenotypes and guide personalized interventions. By outlining current evidence and identifying remaining knowledge gaps, this review offers a strategic framework for precision nutritional care in IBD, positioning diet as a cornerstone of holistic disease management alongside advanced therapies.
Keywords: Body composition, Crohn's disease, inflammatory bowel disease, nutritional screening, ulcerative colitis.

1. Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing–remitting disorders resulting from a complex interaction between genetic susceptibility, immune dysregulation, and environmental triggers.[1,2] With the global rise in IBD prevalence, modifiable factors, such as diet, have emerged as key drivers of disease onset and progression.[1,2] Modern "Westernized" diets—characterized by a high intake of ultra-processed foods (UPF), emulsifiers, and refined sugars—are thought to disrupt the gut-mucosal interface, promoting dysbiosis, impairing the mucus layer, and increasing intestinal permeability.[3-6] This cascade can trigger immune activation in genetically predisposed individuals.[2]

Beyond disease onset, dietary intake can also modify the clinical course of IBD. A Western diet has been reported to increase the risk of disease flares, particularly with red and processed meat, protein, and alcohol, all of which have been associated with a higher risk of relapse.[7] Nutrition plays a crucial role in regulating immune activity. Specific micronutrients and macronutrients—such as amino acids, vitamins, and minerals—directly modulate both innate and adaptive immune responses. For instance, amino acids like arginine and tryptophan are essential for macrophage function and broader immune metabolic pathways.[8,9] Vitamin A is crucial for the maturation of immune cells (e.g., natural killer cells, lymphocytes) and for maintaining mucosal barrier integrity.[10] Similarly, vitamin D modulates adaptive immunity by reducing pro-inflammatory cytokine secretion.[11] Lastly, minerals like zinc and selenium exert anti-inflammatory effects by inhibiting pro-inflammatory immune actions.

This diet-dependent inflammation extends beyond the gut, influencing body composition and metabolic health. It drives changes in insulin sig-

naling, muscle protein turnover, and adipose tissue distribution, which, in turn, affect disease severity.[12] Malnutrition and alterations in body composition are common complications that contribute significantly to morbidity.[13] These changes are particularly seen in the form of sarcopenia (defined as impaired muscle mass and strength)[14] and myosteatosis (characterized by the pathological accumulation of inter- and intramuscular adipose tissue).[15]

Beyond the classical paradigm of malnutrition as an overt caloric deficiency, which still affects a proportion of patients with IBD, an increasingly recognized phenotype is malnutrition associated with excess body weight, often in the form of sarcopenic obesity. In this condition, excess adiposity masks muscle depletion, leading to poorer outcomes.[16] Crucially, nutritional impairment often exists from diagnosis, regardless of disease activity or Body Mass Index (BMI).[17] This highlights the need to shift from reactive supplementation to proactive, systematic nutritional assessment throughout the disease course.[18]

Such comprehensive evaluation lays the groundwork for targeted dietary strategies, which are increasingly recognized for their potential to modulate inflammation, sustain remission, and optimize long-term outcomes. Integrating objective nutritional metrics with therapeutic decision-making positions diet as an essential component of personalized care in IBD.[18] This review aims to critically examine the evolving nutritional challenges in patients with IBD, moving beyond general dietary advice to explore the pathophysiological synergy between nutritional status, body composition, and targeted dietary interventions. By integrating recent clinical evidence and identifying current knowledge gaps, we aim to provide a strategic framework for individualized nutritional care in the era of precision medicine.

2. Methods

This narrative review was synthesized through a comprehensive literature search aimed at identifying the most relevant evidence regarding nutritional assessment, body composition, and dietary interventions in IBD. A structured search was conducted across major electronic databases, including PubMed/MEDLINE, Embase, and the Cochrane Library, from January 2010 to February 2026. The search strategy utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including but not limited to: "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "malnutrition," "nutritional screening," "sarcopenia," "myosteatosis," "myopenia," "body composition," "ultra-processed foods," "inflammatory bowel disease diet," "Exclusive Enteral Nutrition," "Partial Enteral Nutrition," and "Mediterranean diet." Literature was selected based on its clinical relevance to the evolving functional paradigm of IBD management. Selected sources included clinical trials and observational studies investigating the impact of nutrition on disease activity, treatment response, and surgical outcomes, as well as international guidelines and consensus statements. Additionally, pathophysiological evidence from preclinical studies clarifying the role of dietary additives and nutrients in intestinal barrier integrity was incorporated. Priority was given to high-quality, peer-reviewed articles published within the last decade, while landmark studies were also included to provide historical context and a comprehensive understanding of current therapeutic gaps.

3. Nutritional Assessment in the Modern Era: Moving Beyond BMI

Malnutrition in IBD represents a deterioration of physical and mental health due to inadequate intake, often compounded by chronic inflammation.1 Several definitions of malnutrition have been proposed, as outlined in Table 1.

The etiology of malnutrition in IBD is multifactorial. During active disease, oral intake declines due to abdominal pain, nausea, vomiting, and anorexia. Side effects of medications, hospitalization, and long-term dietary restrictions further compound reduced intake. Intestinal mucosal damage from active inflammation leads to malabsorption of iron, folic acid, vitamin B12, vitamin D, and electrolytes.[16] Anemia in IBD is typically multifactorial: iron deficiency anemia (due to chronic blood loss) coexists with anemia of chronic disease, drug-related bone marrow suppression, and anemia secondary to drug-related adverse events.[20] Surgical resection of small bowel segments can precipitate malabsorption by shortening transit time and removing critical absorptive surfaces. Beyond micronutrient deficiency, ileal resection frequently causes bile acid malabsorption, leading to fat malabsorption, steatorrhea, and debilitating diarrhea, further compromising nutritional status.[21]

Notably, a patient can become malnourished even without overt malabsorption, simply due to the catabolic state induced by active inflammation, severe diarrhea leading to fluid and electrolyte depletion, and symptoms that limit eating.[2] Medications play a substantial role: for instance, corticosteroids accelerate muscle catabolism and decrease bone and skin strength, while also causing deficiencies in vitamins D and K, and sulfasalazine inhibits key enzymes for folate absorption.[2]

Over time, this inflammatory-malnutrition axis drives sarcopenia – the loss of muscle mass and strength – which affects 30–55% of patients and is more prevalent in CD than UC.[23] Sarcopenia profoundly impacts clinical outcomes: it reduces quality of life, increases hospital stay length, predicts failure of medical therapies, and raises surgical complication rates.[24]

All patients with IBD are at risk of malnutrition from the time of diagnosis, necessitating routine nutritional evaluation.[25] Studies have demonstrated reductions in both fat-free mass and fat mass in CD patients with longstanding disease, although the influence of factors such as disease location, duration, and phenotype on body composition changes remains incompletely understood and requires further investigation.[23,26] The heterogeneity of existing evidence – with some studies reporting comparable lean mass between CD and UC patients and others showing divergent patterns – underscores the complexity of nutritional assessment in this population.

Crucially, in contemporary IBD management, reliance on BMI is insufficient and potentially misleading. Weight loss and the resulting reduction in BMI are associated with poor prognosis, giving rise to the so-called "obesity paradox," whereby patients with higher BMI appear to experience more favorable outcomes. However, this paradox largely reflects the intrinsic limitations of BMI, which fails to distinguish between lean and fat mass.[27,28] Notably, 15%–40% of adult patients with IBD are classified as obese, and an additional 25%–40% as overweight.[29-33] In this context, excess adiposity often masks concomitant muscle mass depletion, resulting in sarcopenic obesity, a phenotype associated with more severe complications than obesity or sarcopenia alone.[27]

Recognizing this phenotype is essential: skeletal muscle mass plays a critical role in pharmacokinetics by influencing drug distribution and clearance,[34,35] and is a key determinant of postoperative recovery and overall surgical outcomes.[36,37] These observations mandate a paradigm shift: comprehensive nutritional assessment must extend beyond weight-based metrics toward functional characterization that integrates body composition, muscle strength, and physical performance.[38,39]

Table 1. Definitions of Malnutrition According to Different Guidelines

ASPEN*	Requires at least 2 criteria for the diagnosis of malnutrition:
	– Insufficient energy intake
	o Moderate: <75% of estimated energy requirement for ≥1 month
	o Severe: ≤75% of estimated energy requirement for ≥1 month
	– Weight loss
	o Moderate: 5% in 1 month, 7.5% in 3 months, 10% in 6 months, 20% in 1 year
	o Severe: >5% in 1 month, >7.5% in 3 months, >10% in 6 months, >20% in 1 year
	– Loss of muscle mass (e.g., temporalis muscle, pectoralis and deltoids, interosseous muscles, latissimus dorsi, trapezius, quadriceps, and gastrocnemius)
	o Mild or severe
	– Loss of subcutaneous fat (e.g., orbital, triceps, fat overlying the ribs)
	o Mild or severe
	– Localized or generalized fluid accumulation (edema)
	o Mild or severe
	– Reduced hand-grip strength
	o Measurably reduced
ESPEN*	– Body mass index (BMI) <18.5 kg/m²
	Or
	– Weight loss (%)
	o 10% (indefinite period)
	o 5% over the last 3 months
	Combined with either
	– Low BMI (kg/m²)
	o <20 kg/m² if <70 years
	o <22 kg/m² if ≥70 years
	Or
	– Reduced fat-free mass index
	o Men: <17 kg/m²
	o Women: <15 kg/m²
GLIM*	Requires at least 1 phenotypic criterion and 1 etiologic criterion for the diagnosis of malnutrition:
	Phenotypic Criteria:
	– Weight loss (%):
	o 5% within the past 6 months
	o 10% beyond 6 months
	– Low BMI (kg/m²):
	o <20 if <70 years
	o <22 if ≥70 years
	o Asia: <18.5 if <70 years
	o Asia: <20 if ≥70 years
	– Reduced muscle mass
	o Reduced by validated body composition measuring techniques
	Etiologic Criteria:
	• Reduced food intake or assimilation:
	o 50% of energy requirements for >1 week
	o Any reduction for >2 weeks
	o Any chronic gastrointestinal condition that adversely impacts food assimilation or absorption
	• Inflammation:
	o Acute disease/injury
	o Chronic disease-related

ASPEN: American Society for Parenteral and Enteral Nutrition; ESPEN: European Society of Clinical Nutrition and Metabolism; GLIM: Global Leadership Initiative on Malnutrition.

Table 2. Core Differences Among Different Sarcopenia Assessment Frameworks and Their Application in IBD

Framework / Approach	Primary Diagnostic Focus	Key Measures	Strengths	Limitations in IBD
EWGSOP2 *	Muscle strength	Handgrip strength; chair stand test	Clinically intuitive; emphasizes function	Cut-offs derived from geriatric cohorts; may underestimate sarcopenia in younger patients with IBD
SDOC *	Muscle function	Gait speed; physical performance	Strong predictor of disability	Functional testing is often omitted in routine IBD care
GLIM	Malnutrition + Inflammation	Phenotypic (mass loss) + Etiologic (inflammation)	Integrates IBD inflammation as a core criterion	Still requires specific muscle mass cut-offs for IBD
Imaging-based (L3 Morphometry)	Muscle quantity and quality	SMI (CT-derived); Hounsfield Units (HU)	Objective; uses routine scans; linked to drug clearance	Lack of functional data; cut-offs often borrowed from oncology

EWGSOP2: European Working Group on Sarcopenia in Older People; SDOC: Sarcopenia Definition and Outcomes Consortium; IBD: Inflammatory Bowel Disease; SMI: Skeletal Muscle Index; HU: Hounsfield Units.

The clinical implementation of this paradigm, however, faces significant challenges. As detailed in the following sections, the absence of standardized definitions for sarcopenia in IBD (Section 3.1), the emergence of consensus frameworks like GLIM that account for inflammatory burden (Section 3.2), and the availability of opportunistic imaging techniques for precise body composition analysis (Section 3.3) all represent critical pieces of a complex puzzle. Understanding these elements is essential for translating the concept of "nutritional assessment" from theoretical principle into clinical practice – and ultimately for positioning body composition as an integral component of personalized IBD care in the biologic era.

3.1 The Challenge of Diagnostic Heterogeneity

A major hurdle in the clinical management of muscle depletion is the lack of a single, universally accepted definition of sarcopenia, which leads to the use of heterogeneous diagnostic frameworks and considerable variability in the reported prevalence of sarcopenia within the IBD population. Importantly, existing definitions differ substantially in the domains used to characterize sarcopenia. The European Working Group on Sarcopenia in Older People (EWGSOP2) emphasizes low muscle strength, measured as the ability of a muscle to generate force (e.g., handgrip strength), as the primary indicator, whereas the Sarcopenia Definition and Outcomes Consortium (SDOC) prioritizes low muscle function, referring to the capacity to perform physical tasks and movements (e.g., gait speed), as the most clinically relevant predictor of adverse outcomes.[39,40]

In contrast, most IBD-related research focuses on muscle quantity and quality, such as Skeletal Muscle Index and myosteatosis, derived from cross-sectional imaging, often without accompanying functional testing.[13,41] This inconsistency is further compounded by the use of heterogeneous cut-off values, frequently borrowed from oncological or geriatric populations, which may not accurately reflect the metabolic profile of IBD patients.[42] The core differences between these established frameworks are summarized in Table 2, illustrating the importance of an IBD-specific framework that integrates both muscle mass and function in the context of systemic inflammation.

3.2. The GLIM Framework as a Clinical Compass

Inflammatory processes contribute to malnutrition by suppressing appetite and reducing dietary intake, while simultaneously promoting metabolic alterations such as elevated resting energy expenditure and accelerated muscle catabolism. In the context of IBD, intestinal damage further contributes to malnutrition through impaired absorption. The resulting deterioration in body composition, marked by losses in fat-free mass, muscle mass indices, and body cell mass (the metabolically active component of fat-free mass, including muscle and organ cells), is associated with poorer functional capacity and worse clinical outcomes.[43]

Within this context, the implementation of the Global Leadership Initiative on Malnutrition (GLIM) criteria allows for a standardized diagnosis that accounts for the inflammatory burden inherent to IBD.[43,44] The GLIM framework adopts a two-step approach for the diagnosis of malnutrition, beginning with the identification of patients at risk through initial screening using validated tools. The most frequently used tools include general malnutrition screening instruments such as NRS-2002 (Nutritional Risk Screening 2002), MUST (Malnutrition Universal Screening Tool), MST (Malnutrition Screening Tool), as well as IBD-specific tests like the Malnutrition Inflammation Risk Tool (MIRT) and the Saskatchewan IBD–Nutrition Risk (SaskIBD-NR). These tools evaluate factors including recent weight loss, BMI, reduced food intake, and disease impact on nutrition. Patients identified as at risk then undergo a comprehensive diagnostic assessment, including evaluation of phenotypic (weight loss, BMI, muscle mass) and etiologic criteria (inflammation and/or reduced intake or assimilation) as required by the GLIM framework.[45,46]

Unlike earlier tools, GLIM requires the concomitant presence of an etiologic criterion, represented in IBD by the presence of chronic inflammation as well as potentially reduced assimilation, and a phenotypic criterion, identified as non-volitional weight loss or reductions in muscle mass or reduction in BMI. This dual approach allows for a more accurate and clinically meaningful assessment of malnutrition in IBD patients, linking inflammatory burden with functional nutritional status.[47,48]

This diagnostic shift prompts clinicians to transcend simple weight measurements and prioritize tissue quality and composition. Within this framework, traditional markers such as serum albumin need to be reframed: for instance, rather than merely reflecting nutritional deficit, hypoalbuminemia serves as a negative acute-phase reactant, mirroring

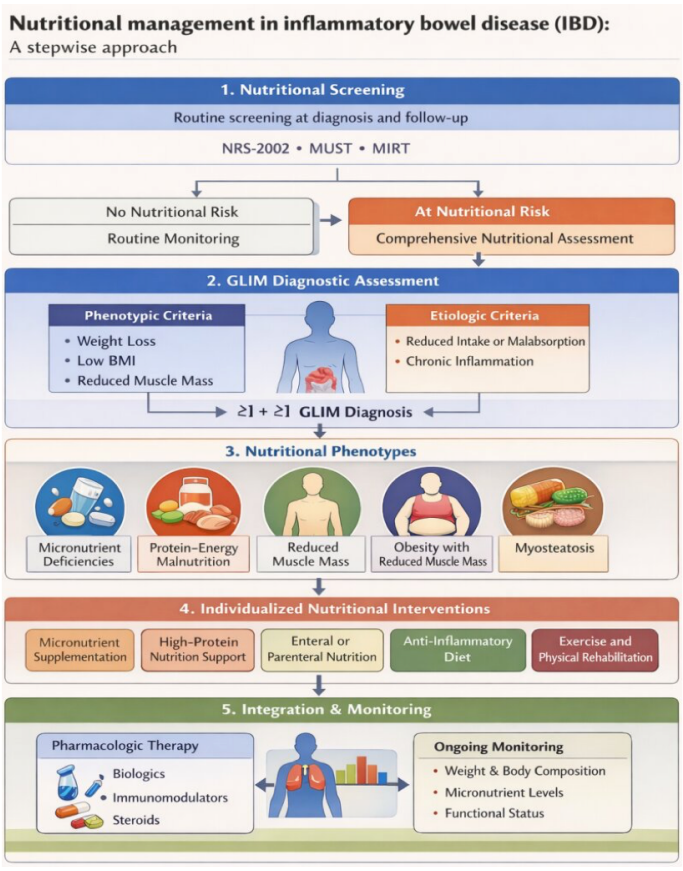

Figure 1. Stepwise Approach to Nutritional Management in Inflammatory Bowel Disease (IBD).
The algorithm begins with routine nutritional screening at diagnosis and follow-up using validated tools (NRS-2002, MUST, MIRT). Patients identified as at nutritional risk undergo a comprehensive assessment according to the Global Leadership Initiative on Malnutrition (GLIM) criteria, which require the simultaneous presence of at least one phenotypic criterion (weight loss, low BMI, or reduced muscle mass) and at least one etiologic criterion (reduced intake/malabsorption or chronic inflammation). The resulting nutritional phenotypes—such as micronutrient deficiencies, protein-energy malnutrition, reduced muscle mass (sarcopenia), obesity with concomitant muscle depletion (sarcopenic obesity), and myosteatosis—guide the selection of individualized interventions. These interventions may include targeted micronutrient supplementation, high-protein nutritional support, enteral or parenteral nutrition, anti-inflammatory dietary strategies (such as the Mediterranean diet, Crohn's Disease Exclusion Diet, or Exclusive Enteral Nutrition), and exercise-based physical rehabilitation. Nutritional care is integrated with pharmacological therapy (biologics, immunomodulators, corticosteroids) and is sustained through ongoing monitoring of weight, body composition, micronutrient levels, and functional status throughout the disease course.

the severity of systemic inflammation and capillary leak rather than protein stores.[18,49] A stepwise algorithm integrating these principles—from initial screening through GLIM-based diagnosis to the identification of distinct nutritional phenotypes and individualized interventions—is proposed in Figure 1.

3.3. Opportunistic Morphometry and the L3 Gold Standard

Computed Tomography (CT) represents an invaluable yet often underutilized resource for body composition analysis in IBD management. Through opportunistic morphometry at the level of the third lumbar vertebra (L3), routine diagnostic scans can be repurposed to objectively quantify the Skeletal Muscle Index (SMI) without additional radiation exposure or cost.[38,42] This approach transcends the inherent limitations of anthropometric measures, providing a high-precision surrogate for total body protein stores.[36,41]

In addition to estimating muscle quantity, L3 morphometry provides radiodensity-based measures (Hounsfield Units) reflecting intramuscular fat infiltration, thereby adding a qualitative dimension to body composition analysis. In IBD, reduced muscle radiodensity has been associated with primary non-response to anti-TNF agents more strongly than BMI, likely reflecting the metabolic consequences of chronic, low-grade systemic inflammation.[35,41]

More recently, ultrasound-based muscle assessment has emerged as a complementary, radiation-free approach for body composition evaluation. Prospective data in IBD cohorts demonstrate that ultrasound-derived measures of the rectus femoris, such as thickness and cross-sectional area, significantly correlate with CT-derived SMI, showing high diagnostic accuracy for sarcopenia detection.[50] This enables bedside assessment of muscle quantity and quality (via echogenicity), providing a dynamic tool for longitudinal monitoring without the constraints of cross-sectional imaging.[50]
These morphometric findings carry profound pharmacokinetic implications. Skeletal muscle constitutes a major determinant of monoclonal antibody distribution; consequently, its depletion is associated with accelerated drug clearance and a shortened biologic half-life.[34] Such pharmacokinetic alterations likely reflect the combined effects of reduced lean distribution volume and persistent inflammatory burden, providing a physiological rationale for sarcopenia-driven variability in drug exposure. Accordingly, patients with significant muscle depletion might benefit from early dose optimization or shortened infusion intervals to maintain therapeutic trough levels and mitigate the risk of secondary loss of response.[51-53] Although prospective validation is required, integrating body composition data into therapeutic drug monitoring (TDM) protocols represents a promising frontier for precision medicine in IBD.

4. Dietary Interventions in IBD

The dietary revolution in IBD has involved a broad recognition of the multifactorial role of diet, not only in managing nutritional needs but also in preventing complications such as sarcopenia and osteoporosis, while simultaneously improving both quality of life and inflammatory disease activity.[54] Consequently, beyond simple nutrient intake, dietary patterns shape intestinal barrier function, microbiota composition, systemic inflammation, and, ultimately, disease activity and remission maintenance.[55] This clinical relevance is supported by robust prospective data: in the PREdiCCt cohort (n=2,629), dietary quality emerged as a primary predictor of disease stability. Specifically, in patients with Ulcerative Colitis, high meat consumption was associated with a significantly increased risk of objective flare (aHR 1.95; 95% CI 1.07–3.56), with relapse rates reaching 26% over two years in the highest intake quartile compared to 12% in the lowest.[56] Mechanistic insights further clarify how specific components drive clinical outcomes. In a randomized, double-blind, placebo-controlled trial involving 60 healthy participants, Wellens et al.[57] first implemented a two-week emulsifier-free diet (EFD), followed by a four-week period of randomized supplementation with either carboxymethylcellulose (CMC), polysorbate-80, carrageenan (CGN), soy lecithin, native rice starch, or placebo delivered through food matrices. The trial revealed that the gut is sensitive to these additives long before inflammation appears; specifically, CMC reduced short-chain fatty acids (SCFAs) levels, and CGN compromised the intestinal barrier, while both triggered subtle shifts in the microbiota. These mechanistic insights into dietary triggers, particularly the det-

rimental role of food additives, have paved the way for the development of targeted exclusion protocols and anti-inflammatory patterns aimed at restoring intestinal homeostasis, the clinical evidence for which is discussed hereafter. Within this framework, distinct dietary strategies can be tailored to specific disease phases and clinical objectives, leading to a nuanced application of the various interventions explored below.[58]

4.1 Diet and Preclinical IBD

Accumulating evidence suggests that dietary patterns preceding disease diagnosis may influence the risk of developing IBD. A comprehensive review evaluating 19 studies with 2,609 IBD patients and 4,000 controls investigated the association between pre-diagnosis dietary intake and subsequent IBD risk. High intake of saturated fats, monounsaturated fatty acids, total polyunsaturated fatty acids (PUFAs), mono- and disaccharides, and meat were associated with increased CD risk; similarly, high intakes of total fats, total PUFAs, and meat increased the risk of UC. On the other hand, dietary fiber and fruits decreased CD risk, and high vegetable intake was protective against UC. Finally, most included studies showed a correlation between high protein intake and IBD risk.[59]

When specific macronutrients are examined separately, the type and quality of fats emerge as particularly relevant. ω-3 PUFAs and long-chain triglycerides exert anti-inflammatory effects, whereas ω-6 PUFAs promote pro-inflammatory responses.6[0] The balance between these fatty acid classes appears critical: animal studies have demonstrated a direct relationship between the arachidonic acid (an ω-6 PUFA) content of inflammatory cell phospholipids and their capacity to produce pro-inflammatory prostaglandin E2 (PGE2). Conversely, feeding with eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA)—both ω-3 PUFAs—reduces PGE2 production and promotes inflammation-resolving mediators.[61,62] These mechanistic insights provide a plausible explanation for the disease-protective effects observed with higher ω-3 PUFA intake.[62]

High consumption of animal protein, particularly red meat, has been consistently associated with increased IBD risk.[63,64] The underlying mechanisms remain incompletely understood but may involve protein-derived metabolites that alter microbiome composition, reduce short-chain fatty acid production, and impact intestinal enterocyte function.[7] Interestingly, while high animal protein intake has been associated with disease exacerbation in UC, this relationship has not been consistently demonstrated in CD, warranting further investigation.[65] Dietary patterns high in refined sugars and low in fiber have also been implicated in IBD pathogenesis.[7] The protective role of dietary fiber, supported by multiple studies, likely reflects its capacity to promote a healthy microbiome, maintain barrier integrity, and modulate immune responses.[66,67]

Collectively, these observations underscore that dietary habits preceding disease onset can meaningfully influence IBD risk. While the precise mechanisms continue to be elucidated, the evidence supports recommendations favoring high fiber intake, adequate fruit and vegetable consumption, limitation of processed meats and refined sugars, and attention to the quality of dietary fats.

4.2. Mediterranean Diet

The Mediterranean diet (MD) is increasingly recognized as a beneficial dietary pattern in IBD,[68] traditionally framed as the anti-inflammatory counterpart to the pro-inflammatory Western lifestyle. However, this conceptual contrast does not automatically translate into definitive evidence supporting the MD as a primary therapy for active disease.[58] Consequently, attention has shifted toward its ability to modulate gut microbial diversity and promote the production of anti-inflammatory metabolites. This is particularly relevant given the limitations of current pharmacological therapies.[69] Nutritional interventions such as the MD emerge as potentially valuable non-pharmacological adjuncts, targeting complementary inflammatory and microbial pathways not fully addressed by current advanced therapies.[70] Recent trials have moved beyond observational studies to evaluate the MD as a structured therapeutic intervention.

The clinical efficacy of MD was robustly assessed in the DINE-CD randomized trial (n=191), a multicenter study comparing the MD against the more restrictive Specific Carbohydrate Diet (SCD), a dietary regimen that eliminates lactose (but not dairy products), sucrose, starchy vegetables (including most legumes), and all grains, in adults with mild-to-moderate CD (defined by a short Crohn's Disease Activity Index [sCDAI] score of 176–399).[71]

The primary outcome of symptomatic remission at week 6 was achieved by comparable proportions in both groups (43.5% in the MD group vs. 46.5% in the SCD group, P = .77), with a similar pattern observed for fecal calprotectin response at week 6 (30.8% for MD vs. 34.8% for SCD, P = .83). Notably, both groups exhibited markedly low rates of C-reactive protein (CRP) normalization. These findings underscore that the MD represents an effective and feasible strategy for symptom management and quality-of-life improvement in CD,[71] even though its impact on biochemical markers appears modest. These biological pathways are consistent with multi-omic analyses, where higher MD adherence associates with the enrichment of beneficial bacteria, favorable shifts in microbial metabolites, and lower inflammatory activity.[72] These microbiota changes correlate inversely with inflammatory markers such as fecal calprotectin, suggesting that diet-driven microbial metabolism contributes to clinical outcomes.[73]

In a 2025 prospective study including 271 patients with newly diagnosed CD, adherence to the MD was correlated with a noncomplicated CD course and lower clinical and biochemical disease activity, as well as reduced dysbiosis. Mechanistically, the MD was linked to an enrichment of SCFA-producing bacteria (Faecalibacterium) and a reduction of species associated with CD (Escherichia coli and Ruminococcus gnavus), alongside a shift towards increased production of anti-inflammatory metabolites and decreased levels of tryptophan metabolites, ceramides, and primary bile acids.[74]

Evidence supporting the MD is emerging also in UC. In a prospective trial enrolling adults with quiescent UC, participants were randomized to either the MD pattern or the Canadian habitual dietary pattern for 12 weeks. During the study period, loss of clinical response was experienced by a significantly higher proportion of patients following the habitual diet group compared to the MD group (31% vs. 13%, P = 0.003), and 75% of patients in the habitual diet exhibited elevated fecal calprotectin (>100 μg/g) compared to 20% in the MD group at week 12. Notably, adherence to the MD was associated with an anti-inflammatory signature in both fecal metabolites (higher total fecal short-chain fatty acids, including acetic and butyric acids) and microbiota composition (increased abundance of Alistipes finegoldii, Flavonifractor plautii, and Ruminococcus bromii).[75] Furthermore, a recent study observed that adherence to the MD was associated with reduced CRP and fecal calprotectin in UC, an effect mediated through reduced dysbiosis.[76]

Overall, the biological rationale for these clinical improvements lies in

the MD's provision of a diverse array of microbiota-accessible carbohydrates, polyphenols, and unsaturated fatty acids that support a healthy gut ecosystem, wherein anti-inflammatory benefits appear to be mediated mainly through selective enrichment of SCFA-producing taxa and associated metabolic pathways, increased microbial richness, and reduced dysbiosis. Specifically, SCFAs, including acetate, butyrate, and propionate, play central roles in modulating immune responses, enhancing epithelial barrier function, and suppressing pro-inflammatory signaling pathways.[77] Collectively, this evidence supports the potential of the MD as a foundational, adjunctive dietary strategy, promoting mucosal homeostasis and complementing pharmacological interventions, particularly for remission maintenance and long-term metabolic health.[68,71,73]

4.3 Exclusive and Partial Enteral Nutrition

Perhaps the largest body of literature on dietary therapy in IBD evaluates exclusive enteral nutrition (EEN), a complete exclusion diet in which patients receive 100% of their caloric intake from formula rather than table foods. EEN can be administered using intact protein, semi-elemental, or elemental formulations, tailored to meet the patient's nutritional requirements.[78] Metagenomic studies have demonstrated that EEN induces rapid and profound changes in the intestinal microbiome, observable as early as one week after initiation.[79] This pattern was reflected in a prospective case–control study of 15 children with CD, in which EEN induced a decline in fecal microbial diversity, including reductions in key commensal taxa, changes that were associated with improvements in clinical disease activity and decreases in inflammatory markers.[80] Notably, these microbiome changes are more pronounced in patients who respond to EEN compared with non-responders, indicating a potential microbial susceptibility.[78]

Clinically, EEN has been shown to improve symptoms, mucosal healing, and nutritional status in pediatric CD, achieving remission rates comparable to corticosteroids. In randomized trials comparing EEN with steroids, both therapies improved clinical symptoms and systemic inflammatory markers, but EEN conferred superior mucosal healing.[81] Similar clinical results have not been reproduced in adults, as EEN resulted in lower rates of clinical response compared with steroids, which may reflect differences in patient adherence rather than intrinsic efficacy.[82]

While EEN is highly effective for the induction of remission, long-term adherence is challenging. A seminal 2006 study in pediatric patients with CD showed that partial enteral nutrition (PEN), providing 50% of daily calories, halved the 2-year relapse rate compared to a free diet (aHR 0.40, 95% CI 0.15-0.98), supporting its role as a maintenance treatment.[83] However, a subsequent study indicated that PEN is inferior to both EEN and anti-TNF for inducing remission in pediatric CD.84 Of note, retrospective evidence suggests that the effectiveness of PEN increases when 80-90% of calories are delivered.[85] Finally, a 2026 open-label randomized trial compared cyclic EEN (administered for 2 weeks every 8 weeks) with PEN in pediatric patients with CD who had achieved clinical remission following EEN induction. Over 12 months of follow-up, cyclic EEN was superior to PEN in reducing relapse risk (aOR 0.29, 95% CI 0.13–0.70), while tolerance to enteral nutrition was excellent, reaching 100% in both groups.[86]

The restrictive nature of EEN has motivated the development of whole-food–based diets, such as CD-TREAT and CDED, which aim to replicate EEN's anti-inflammatory effects while improving long-term acceptability and adherence.

4.4. Solid-Food Alternatives to EEN: From CD-TREAT to Exclusion Diets

Building upon the paradigm of EEN, efforts have increasingly focused on developing solid food-based strategies capable of reproducing its anti-inflammatory effects while improving long-term acceptability. Along this continuum, the Crohn's Disease Treatment-with-EATing (CD-TREAT) diet represents a novel, mechanistically driven approach designed to mimic the nutritional composition of EEN using whole foods—selectively excluding gluten, lactose, and alcohol while matching fiber levels.[87]

CD-TREAT was initially evaluated against EEN in a crossover study focusing on tolerability and microbial shifts: in a randomized controlled trial (RCT) involving 25 healthy adults, CD-TREAT demonstrated higher acceptability, while multi-omic analyses confirmed that both diets induced comparable shifts in the gut microbiome and metabolome.[87] Its anti-inflammatory effect was further validated in HLA-B27 transgenic rats, where a 4-week intervention significantly reduced histopathological ileitis severity ($P = 0.044$) to a degree comparable with EEN. These findings translated into a pediatric pilot trial ($n = 5$): after 8 weeks, 80% of children achieved clinical response and 60% reached remission, with a significant reduction in fecal calprotectin.[87]

While CD-TREAT aims to reproduce the EEN paradigm, other approaches prioritize selective exclusion of modern dietary components implicated in intestinal inflammation. The Crohn's Disease Exclusion Diet (CDED) addresses this by limiting exposure to ultra-processed foods, emulsifiers, and refined sugars—components directly linked to gut barrier disruption and dysbiosis.[88] The efficacy of the CDED is rooted in a profound microbial and metabolic reset, characterized by a significant reduction in Proteobacteria (specifically *E. coli*) and a favorable shift in tryptophan metabolism, marked by decreased fecal kynurenine and increased indole generation, a signature associated with sustained remission.[89] The seminal study by Levine et al.[90] enrolled 78 pediatric patients with mild-to-moderate CD randomized to EEN or CDED with 50% PEN. While efficacy at week 6 was comparable, CDED + PEN demonstrated significantly higher tolerability (OR 13.92, 95% CI 1.68-115.14); notably, following the introduction of a free diet in the EEN group complemented with 25% PEN, week-12 steroid-free clinical remission rates were inferior compared to CDED + 25% PEN, and adherence strongly correlated with clinical outcomes across both regimens. Subsequently, a randomized controlled trial in 44 adults with mild-to-moderate CD showed that CDED + PEN and CDED alone were similarly effective in inducing remission at week 6, with comparable sustained remission rates at week 28 and parallel reductions in CRP and fecal calprotectin.[88]

The Specific Carbohydrate Diet (SCD) represents an alternative, more restrictive nutritional approach. By excluding disaccharides and most polysaccharides, the SCD aims to limit the substrates available for potentially pro-inflammatory gut bacteria, shifting the microbial environment.[71,91] This is achieved through a strict biochemical selection that permits unprocessed meats, fresh fruits, and honey, while categorically restricting all grains, starchy vegetables (e.g., potatoes, yams), and industrial sweeteners.[71] Clinically, while the SCD has demonstrated the potential for deep remission, with small pediatric cohorts showing complete endoscopic healing in up to 40% of cases,[92] data from the DINE-CD trial in adults showed that it was not superior to the Mediterranean Diet in terms of symptomatic remission, fecal calprotectin response, or CRP response.[71]

While both CDED and SCD show therapeutic promise, they share the challenge of a high adherence burden. The risk of nutritional deficiencies and restrictive eating behaviors necessitate structured, multidisciplinary monitoring to ensure that the clinical benefits of "nutritional prehabilitation" and inflammatory control are not compromised by long-term sustainability issues. Addressing this limitation, the Tasty&Healthy (T&H) diet—a whole food diet that excludes processed food, gluten, red meat, and dairy, without requiring formula or mandatory ingredients—has recently been evaluated in children and young adults with CD. Compared to EEN, the T&H diet demonstrated superior tolerability (aOR 7.7, 95% CI 2.4-25.0), with comparable clinical and biochemical efficacy.[93]

Although most solid-food dietary strategies have been developed for Crohn's disease, similar exclusion-based approaches are increasingly being investigated in ulcerative colitis. The CRAFT UC trial (n=62) further underscores the power of targeted nutrition in refractory patients (50% of them had previously failed biologic therapies). This study evaluated the effect of the UC Exclusion Diet (UCED) alone versus standard Fecal Transplantation (FT) with or without diet modification. Remarkably, the UCED alone outperformed standard FT for steroid-free clinical remission (40% vs. 12% and 21% in the FT groups without and with UCED; $P < 0.05$ for both comparisons). Moreover, the UCED was the only intervention to achieve complete mucosal healing (Mayo 0: 20% vs. 0% in both FT groups, $P = 0.022$) and demonstrated superior safety for preventing exacerbations (6.7% vs. 21.1%) and maintaining response at week 12.94 Nevertheless, these findings should be interpreted with caution given the uncertain efficacy of FT in UC.

4.5. Fasting-Mimicking Diets: A Novel Approach

A key barrier to the therapeutic use of diet in IBD is the challenge of sustaining long-term dietary changes, as evidenced by low adherence rates across interventions. Fasting-mimicking diets (FMD) offer an attractive solution, as they do not require patients to modify their baseline diet continuously. FMD consists of short cycles, typically 5 consecutive days per month, of a plant-based, calorie-restricted regimen that is low in calories, sugars, and protein, but relatively high in unsaturated fats, designed to mimic the physiological benefits of fasting. Patients consume their usual diet for the remainder of the month, and cycles can be repeated over several months.[95]

Preclinical studies in mouse models of colitis have demonstrated that FMD promotes intestinal regeneration, modulates the gut microbiota (notably increasing Lactobacillaceae), reduces inflammatory cytokine expression, and supports mucosal healing. In healthy human volunteers, multiple 5-day FMD cycles improved metabolic parameters and reduced mildly elevated C-reactive protein levels, supporting systemic anti-inflammatory effects.[95]

The first randomized controlled trial in patients with mild-to-moderate CD evaluated the safety and efficacy of short-term FMD cycles (n = 97 patients). Compared with controls, a higher proportion of patients in the FMD group achieved the primary endpoint of CDAI-based clinical response (69.2% vs. 43.8%, $P = 0.03$), as well as clinical remission (CDAI ≤150; 64.6% vs. 37.5%, $P = 0.02$). In addition, the FMD group experienced a significant reduction in fecal calprotectin levels (−22.0%), whereas levels increased in the control group (+8.0%; $P = 0.03$).[96]

Periodic fasting-mimicking diets (FMD) may offer a complementary approach to conventional therapy, supporting remission maintenance through improvements in mucosal integrity and metabolic resilience. When paired with the Mediterranean diet during refeeding periods, FMD could further benefit from the diet's anti-inflammatory properties and ability to reinforce gut barrier function.[96] While promising, this approach remains investigational, and further studies are needed to define optimal cycle duration, frequency, and patient selection criteria.

4.6. Nutritional Strategies in the Postoperative Setting: Preoperative Support and Recurrence Prevention

Patients with IBD frequently require surgery during their disease course, and many present with pre-existing nutritional deficits that increase perioperative risk. The identification of sarcopenia and malnutrition through the assessment frameworks discussed in Section 3 carries particular prognostic significance in this setting: patients with weight loss exceeding 10% in the preceding six months, BMI below 18.5 kg/m², hypoalbuminemia, or Nutritional Risk Screening (NRS) score >5 face substantially higher rates of perioperative complications.[97] These observations underscore the importance of preoperative nutritional optimization as a form of "nutritional prehabilitation."

Preoperative nutritional support is strongly recommended, particularly in malnourished CD patients awaiting surgery.[97,98] Systematic reviews have identified preoperative nutritional status as a predictor of postoperative hospital stay length, with serum albumin representing a prognostic factor for complication risk.[99] In patients with severe metabolic risk, preoperative nutritional therapy may be beneficial. Enteral nutrition should be preferred when feasible, with parenteral support reserved for cases where enteral feeding is contraindicated or insufficient. Nutritional status should be reassessed postoperatively to guide ongoing support.

Postoperative recurrence prevention represents a critical extension of these concepts, particularly in CD. Following surgical resection, the intestinal microenvironment remains highly susceptible to inflammatory triggers that can drive early endoscopic recurrence at the anastomotic site.[100] The dietary strategies discussed throughout Section 4 find specific application in this vulnerable period.

In the immediate postoperative period, exclusive enteral nutrition (EEN) has emerged as a potent "bridging therapy" to mitigate this risk. A recent randomized controlled trial including 100 patients demonstrated that postoperative EEN significantly reduces endoscopic recurrence rates of CD (defined as Rutgeerts score ≥ i2) compared to early introduction of a standard solid diet (Relative Risk [RR] 0.474; 95% CI 0.238-0.944; $P = 0.026$).[101] By providing total bowel rest from dietary antigens while ensuring optimal nutrient delivery, EEN facilitates early mucosal stabilization and supports the structural integrity of the anastomosis.[101]

Following this initial stabilization, long-term dietary quality becomes the primary determinant of sustained remission. A landmark multicenter prospective cohort study, evaluating 520 food diaries from 103 patients, highlighted that higher dietary intake of micronutrients typically abundant in the Mediterranean Diet, such as isoflavones, provitamin A, and specific antioxidants, is significantly associated with a reduced risk of long-term endoscopic postoperative recurrence (defined as Rutgeerts score ≥ i2a).[100]

Collectively, these findings support a stratified postoperative nutritional approach, beginning with targeted enteral support via EEN to promote early mucosal recovery, and transitioning to a Mediterranean-style diet enriched with key micronutrients to prevent the progression from subclinical inflammation to clinical recurrence.[68,100-102]

4.7. Synthesis and Practical Considerations

Effective dietary management in IBD requires a personalized, phase-specific approach. During active flares, exclusion diets, most notably the CDED, can mitigate dietary triggers of inflammation, support gut barrier recovery, and enhance anabolic and immune responses in synergy with pharmacological therapy.[88] In the remission phase, adherence to the Mediterranean diet helps maintain a balanced gut microbiome, promotes metabolic homeostasis, and preserves mucosal integrity, while periodic fasting-mimicking interventions may further enhance mucosal regeneration and systemic resilience.[68,95]

Optimal dietary management integrates these strategies within a personalized, phase-specific framework that accounts for disease activity, nutritional status, body composition, and adherence potential. Tailoring interventions to the patient's clinical context allows clinicians to complement pharmacological therapy, improve long-term gut health, and support functional recovery.

Collectively, these dietary approaches provide a foundational layer of nutritional modulation, translating mechanistic insights into real-world care. Aligning nutritional strategies with disease phase and metabolic status, as summarized in Table 3, ensures that diet not only supports therapy but also contributes to sustained patient well-being.

5. Synchronizing Nutrition and Pharmacology: Towards an Integrated Therapeutic Strategy

Nutrition and pharmacological therapy in IBD should not be viewed as alternative interventions, but rather as complementary and interdependent tools. Diet can influence drug responsiveness, while effective pharmacological control of inflammation creates the biological conditions necessary for nutritional interventions to exert their full therapeutic potential. In this framework, nutrition and drugs act synergistically, with the potential to mutually reinforce their clinical effects.

While dietary patterns can directly modulate intestinal inflammation, their therapeutic potential is likely maximized when synchronized with pharmacological therapy. Crucially, nutritional interventions should be considered as complementary to advanced medical therapies both during induction and maintenance phases, with the potential to enhance therapeutic efficacy.

In a prospective open-label study enrolling 56 adult patients with CD, the combination of adalimumab plus partial enteral nutrition (PEN) was superior to adalimumab alone in inducing both clinical and endoscopic improvement.[103] Consistently, a larger retrospective cohort study including 197 patients showed that, compared with biologic therapy alone, the combination of biologics and EEN was associated with higher rates of both clinical and endoscopic response at weeks 16 and 52.104 Another retrospective study evaluating the addition of PEN to treatment escalation in patients with CD who had lost response to biologics reported significantly higher rates of clinical response (64% vs. 25%, P = 0.03) and transmural response (65% vs. 25%, P = 0.03) at week 24 in patients receiving combination therapy.[105]

A pilot RCT (n = 32) evaluated the adjunctive use of a FMD in patients with UC initiating advanced therapies. Although the study terminated earlier due to the COVID-19 pandemic and was underpowered to

Table 3. Dietary Strategies in Inflammatory Bowel Disease: A Comparative Overview

Dietary Intervention	Disease Setting	Main Indication	Key Characteristics	Evidence Level	Feasibility / Adherence
Mediterranean Diet (MD)	CD and UC	Remission maintenance; adjunct in mild disease	Balanced, whole-food diet, rich in fiber polyphenols, and unsaturated fats	RCTs and prospective cohorts	High
Exclusive Enteral Nutrition (EEN)	Primarily pediatric CD; selected adults	Induction of remission; steroid-sparing therapy	100% liquid formula; complete exclusion of table foods for 6–8 weeks	Strong (especially pediatric RCTs)	Low–moderate
Partial Enteral Nutrition (PEN)	CD	Maintenance of remission	~50% calories from formula plus regular diet	Moderate	Moderate
CD-TREAT	CD	Alternative to EEN	Whole-food diet mimicking EEN macro- and micronutrient composition	Pilot clinical studies	Moderate–high
Crohn's Disease of remission Exclusion Diet (CDED)	Mild–moderate CD cohorts)	Induction and maintenance	Exclusion of ultra-processed foods; phased diet combined with PEN	RCTs (pediatric and adult)	Moderate
Specific Carbohydrate Diet (SCD)	CD (mainly pediatric	Induction of remission	Elimination of grains, lactose, refined sugars	Small trials and cohorts	Low
Fasting-Mimicking remission maintenance Diet (FMD)	Mild–moderate CD	Adjunctive therapy; plant-based diet	Short, cyclic, calorie-restricted	Emerging RCT evidence	High (short cycles)
Postoperative EEN + MD	Post-surgical CD	Prevention of recurrence	Short-term EEN followed by MD	RCTs and prospective studies	Moderate
UC Exclusion D iet (UCED)	Mild–moderate ulcerative colitis	Induction of remission	Exclusion of dietary components associated with barrier disruption and dysbiosis	RCT (CRAFT UC trial)	Moderate

demonstrate a statistically significant difference in clinical response at week 8 (57% vs. 35% in favor of the FMD, P = 0.11), exploratory analyses of secondary endpoints suggested greater clinical improvement and higher rates of successful steroid tapering by week 8 in the dietary intervention group.[106]

Collectively, these findings underscore that dietary modulation is not merely a supportive measure but an active modifier of disease pathophysiology. The goal of nutritional therapy in IBD has evolved beyond caloric replacement toward the restoration of gut barrier integrity and skeletal muscle function.18 Integrating nutritional interventions and pharmacological strategies may therefore represent a promising approach to overcome the current therapeutic ceiling, in line with the notion that the patient's metabolic state can substantially influence drug efficacy.[107]

A major barrier to nutritional recovery in IBD is inflammation-induced anabolic resistance, characterized by impaired protein synthesis by the skeletal muscle, despite adequate amino acid availability.[108] During flares, pro-inflammatory cytokines—notably tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)—impair the Akt–mTORC1–p70S6K signaling pathway, thereby blunting the anabolic response to dietary protein intake. In this context, nutritional strategies based solely on high protein intake may be insufficient to restore muscle protein synthesis.[109]

Indeed, effective nutritional rehabilitation necessitates temporal coordination with pharmacological therapies, generating a "therapeutic window" in which the suppression of inflammatory signaling permits reactivation of mTORC1-dependent anabolic pathways, thereby restoring muscle sensitivity to nutritional stimuli.[108] Targeted biological therapies, particularly anti-TNF agents, appear to play a pivotal role in releasing this "inflammatory brake," enabling protein supplementation to exert its intended anabolic effects.[35,110] The mechanisms underlying this inflammatory blockade and its subsequent therapeutic restoration are summarized in Figure 2.

Finally, this integrated strategy requires systematic elimination of dietary factors capable of sustaining low-grade intestinal inflammation. Specific emulsifiers found in ultra-processed foods, such as carboxymethylcellulose (CMC) and polysorbate-80 (P80), have been shown to impair mucus barrier function and promote metabolic endotoxemia.[111] Their exclusion may help mitigate persistent low-grade inflammation that otherwise compromises mucosal healing and muscle protein synthesis.[90]

5.1 Supplementation

The successful restoration of muscle protein synthesis and functional capacity requires not only inflammatory control but also the correction of specific micronutrient deficits that are nearly ubiquitous in IBD. These deficiencies act as metabolic brakes, limiting the efficacy of both nutritional interventions and pharmacological therapy. Accordingly, supplementation should be viewed not as an isolated intervention but as an integral component of the induction-to-rehabilitation framework outlined above.

Iron deficiency affects approximately 45% of patients and arises from chronic blood loss, mucosal damage, decreased absorption, and inadequate oral intake.[112] Diagnosis requires interpretation in the context of inflammation: ferritin <30 µg/L in the absence of active inflammation, or ferritin <100 µg/L with transferrin saturation <20% in the presence of inflammation, confirms iron deficiency anemia and warrants prompt

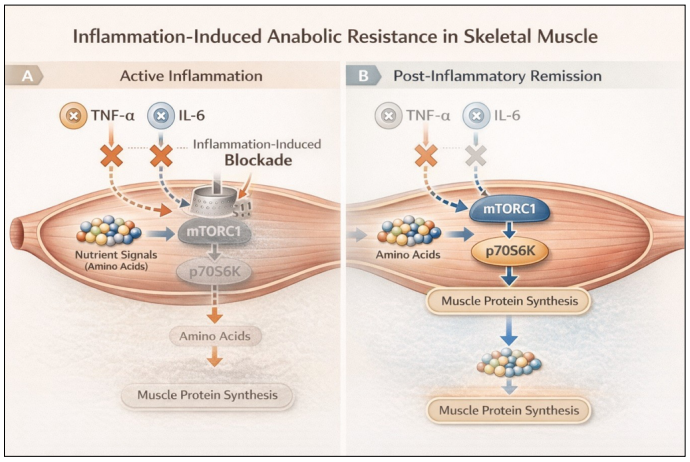

Figure 2. Inflammation-Induced Anabolic Resistance in Skeletal Muscle. During active inflammation, pro-inflammatory cytokines impair Akt–mTORC1 signaling, blunting the anabolic response to amino acid availability. Following inflammatory remission, restoration of mTORC1 activity permits effective stimulation of muscle protein synthesis.

correction.[112] Iron replacement can be administered orally or intravenously. In patients who are clinically, endoscopically, and biochemically in remission with mild anemia (hemoglobin >10 g/dL), oral iron may be sufficient. However, intravenous iron is recommended for severe iron deficiency (hemoglobin <10 g/dL), intolerance or unresponsiveness to oral therapy, and in the presence of active inflammation.[113] Specific considerations on the role of iron in metabolism are discussed in Section 5.2.

Vitamin B12 and folate deficiencies are common in IBD, particularly following uncontrolled inflammation, extensive small bowel resection, or methotrexate and sulfasalazine use.[15] These deficits manifest as macrocytic anemia and should be actively screened. B12 replacement should be administered parenterally when deficiency is confirmed, while weekly folic acid supplementation is recommended for at-risk patients.[15]

Vitamin D deficiency is highly prevalent in IBD and carries particular significance given its immunomodulatory role and impact on bone health. IBD patients have an increased fracture risk compared to healthy individuals, further elevated by glucocorticoid use and vitamin D depletion.[15] Target 25(OH)D levels should exceed 30 ng/mL, achievable through sunlight exposure, dietary intake (oily fish, liver, egg yolks), and supplementation – with some studies suggesting that up to 10,000 IU daily may be required in selected patients.[11]

ω-3 fatty acids merit consideration based on their anti-inflammatory properties, discussed in Section 4.1. IBD patients may exhibit essential fatty acid deficiencies, and supplementation with fish or olive oil-derived ω-3s may improve oxidative stress profiles, support mucosal healing, and potentially reduce the long-term risk of colorectal neoplasia.[115] However, no specific recommendations on their supplementation can be made based on current evidence.

Importantly, these supplementation strategies should not be applied in isolation. Iron deficiency frequently coexists with other deficits, and optimal metabolic recovery requires a multi-nutrient approach that includes B vitamins, zinc, selenium, and vitamin D. Recognizing these interconnected patterns allows supplementation to be integrated into a comprehensive nutritional plan—ensuring that the correction of individ-

ual deficits synergistically supports the restoration of anabolic responsiveness, mitochondrial function, and ultimately, physical resilience.

This integrated view of supplementation naturally leads to a deeper consideration of iron's unique role as a bioenergetic catalyst—a concept explored in the following section, where we examine how iron deficiency and its correction intersect with the pathways of anabolic resistance and metabolic recovery outlined in Figure 1.

5.2 Iron as a Bioenergetic Catalyst: The Energetic Counterpart to Anabolic Resistance

While suppression of the Akt–mTORC1 pathway reflects impaired muscle protein synthesis, inflammation-induced disruptions in iron metabolism constitute a critical limitation in muscle bioenergetics. Effective functional recovery therefore requires not only the restoration of anabolic signaling but also the availability of sufficient metabolic substrate to support tissue repair and contractile activity.[116]

In this context, iron deficiency in IBD should be viewed not merely as a hematological issue but as a critical constraint on mitochondrial energy production.[117] Iron is an essential cofactor for key components of the electron transport chain, including cytochromes and iron-sulfur cluster-containing enzymes; consequently, even subclinical iron deficiency can impair cellular energy production independently of hemoglobin levels.[116]

During systemic inflammation, the upregulation of hepcidin induces a state of functional iron deficiency by sequestering iron within the reticuloendothelial system and limiting its intestinal absorption.[118] Under these conditions, oral iron supplementation is ineffective and sometimes deleterious, as unabsorbed luminal iron can exacerbate dysbiosis, promote oxidative stress, and further amplify mucosal inflammation.[119-121] In contrast, early intravenous (IV) iron administration bypasses inflammation-induced sequestration and is more effective than oral iron in correcting iron deficiency in patients with active IBD. By rapidly replenishing bioavailable iron pools, IV iron supports metabolic recovery in high-turnover tissues.[122] This is particularly relevant for the regenerating intestinal epithelium and metabolically active skeletal muscle, where adequate iron availability supports oxidative metabolism required for tissue repair and functional recovery.[120] IV iron priming may act as a metabolic enabler, enhancing muscular endurance, reducing fatigue, and supporting the restoration of anabolic responsiveness.[123] Speculatively, in selected patients with active inflammation, early IV iron therapy could be considered an integral component of personalized nutritional and metabolic rehabilitation during induction.[117-120]

Importantly, the success of metabolic recovery requires a multi-nutrient approach, as iron deficiency frequently coexists with other deficits. Observational evidence indicates that low serum vitamin D status is common in patients with IBD and is associated with increased odds of clinically active disease, mucosal inflammation, clinical relapse, and lower quality-of-life scores, compared with patients with higher vitamin D levels. This suggests a correlation between hypovitaminosis D and adverse clinical outcomes in this population.[124]

Recognizing these interconnected patterns allows supplementation strategies to be integrated into a comprehensive nutritional plan, ensuring that the correction of iron deficiency is synergistically supported by other targeted micronutrients (e.g., B vitamins, zinc, selenium) to ultimately optimize metabolic recovery and response to therapy.[125,126]

CONCLUSION

Nutritional status is increasingly recognized as a pivotal determinant of therapeutic outcomes in IBD, as chronic inflammation profoundly affects both systemic metabolism and body composition. Moving beyond traditional weight-based metrics, the functional assessment of muscle mass, quality, and overall body composition provides a more accurate risk stratification and a clearer understanding of the metabolic consequences of the disease. This holistic, patient-centered approach has the potential not only to optimize treatment efficacy but also to improve long-term physical function, quality of life, and the likelihood of achieving durable, deep remission.

Diet is emerging as an important—and still underappreciated—modulator of intestinal inflammation and epithelial barrier integrity. Growing evidence implicates ultra-processed foods and dietary additives in the persistence of low-grade inflammation, providing a strong rationale for targeted nutritional interventions to control disease activity.

The integration of standardized nutritional screening tools that account for both inflammatory burden and body composition enables early identification of distinct nutritional phenotypes, allowing clinicians to move beyond reactive supplementation toward proactive, individualized care. When combined with validated diagnostic frameworks such as the GLIM criteria, these tools facilitate a precision medicine approach in which therapeutic decisions are informed by the patient's metabolic reserve, inflammatory status, and functional capacity. Available evidence supports a phase-specific framework for nutritional management in which dietary and metabolic interventions are strategically aligned with disease activity and pharmacological treatment (Table 4). Rather than treating nutrition and drugs as independent domains, this model emphasizes their bidirectional interaction across the disease course. During

Table 4. An Induction-to-Rehabilitation Framework for Nutritional Management in Adult IBD

Clinical Phase	Pathophysiological Target	Representative Interventions
Baseline Assessment	Body composition (sarcopenia) and nutritional risk	Functional evaluations and imaging techniques (e.g., opportunistic L3-CT morphometry to derive skeletal muscle index) allow for a more precise understanding of a patient's metabolic reserve and may predict patient frailty
Induction Phase (inflammatory flares)	Systemic and intestinal inflammation, inflammation-driven anabolic resistance	Nutritional interventions as adjunct or alternative to pharmacological control of inflammation ± early micronutrient repletion (e.g., intravenous iron) in selected patients
Rehabilitation Phase the achievement of symptomatic control)	Nutritional deficits, muscle and functional recovery	Dietary strategies limiting exposure to ultra-processed foods and food (after emulsifiers to reduce relapse risk, targeted protein and caloric supplementation, micronutrient repletion

inflammatory flares, pharmacological suppression of pro-inflammatory cytokines creates a therapeutic window in which nutritional interventions can overcome anabolic resistance and restore metabolic function. Conversely, the elimination of pro-inflammatory dietary factors and the correction of micronutrient deficiencies may reduce the inflammatory burden that drives both disease activity and treatment failure. This synergy positions nutrition not as a supportive measure but as an active modifier of disease pathophysiology. Translating this evidence-based framework into clinical practice requires adherence to several key principles. The following actionable recommendations synthesize the current state of knowledge and provide a roadmap for integrating nutritional assessment and intervention into routine IBD care:

1. Screen early and systematically. All patients with IBD should undergo nutritional screening at diagnosis and at regular intervals thereafter, using validated tools (e.g., NRS-2002, MUST, or IBD-specific instruments such as MIRT or SaskIBD-NR), followed by GLIM-based diagnostic assessment when risk is identified.

2. Look beyond BMI. Body composition analysis (through opportunistic CT morphometry at the L3 level or bedside ultrasound assessment) should be integrated into routine evaluation to identify sarcopenia, myosteatosis, and sarcopenic obesity, which carry prognostic and pharmacokinetic implications that BMI alone cannot capture.

3. Align diet with disease phase. During active disease, exclusion-based strategies (CDED, EEN) can serve as therapeutic adjuncts or, in selected mild-to-moderate cases, as primary interventions. During remission, adherence to a Mediterranean-style dietary pattern should be encouraged to support microbiota diversity, mucosal integrity, and metabolic health.

4. Correct micronutrient deficiencies proactively. Iron, vitamin D, vitamin B12, folate, zinc, and selenium status should be monitored and corrected in a coordinated, multi-nutrient approach. In the presence of active inflammation, intravenous iron should be preferred over oral supplementation.

5. Integrate nutrition with pharmacological strategy. Nutritional interventions should be temporally coordinated with biologic therapy to exploit the therapeutic window created by inflammatory suppression, thereby overcoming anabolic resistance and maximizing the efficacy of both dietary and pharmacological approaches.

6. Minimize pro-inflammatory dietary exposures. Patients should be counseled to reduce intake of ultra-processed foods, dietary emulsifiers, and refined sugars, which have been implicated in barrier disruption, dysbiosis, and persistence of low-grade inflammation.

This review has several limitations that warrant acknowledgment. As a narrative synthesis, the selection of studies was not conducted through a systematic, pre-registered protocol, which introduces the possibility of selection bias. A substantial proportion of the evidence supporting dietary interventions derives from pediatric cohorts, and its transferability to adult patients remains incompletely established. Looking forward, several key questions remain. The optimal timing, duration, and composition of dietary interventions across different disease phenotypes require further clarification through adequately powered randomized controlled trials. The role of body composition as a predictor of drug exposure and therapeutic efficacy warrants prospective validation, as does the potential benefit of early intravenous iron repletion in mitigating inflammation-driven metabolic dysfunction. The development of IBD-specific definitions of sarcopenia and myosteatosis, validated against clinically meaningful outcomes, represents an urgent research priority. Finally, the long-term impact of sustained adherence to anti-inflammatory dietary patterns on mucosal healing, structural bowel damage, and the trajectory of disease progression remains to be established. In conclusion, effective management of IBD extends beyond symptomatic control and immunomodulation to encompass the restoration of metabolic health, preservation of skeletal muscle function, and sustained nutritional resilience. By recognizing nutrition as a cornerstone of personalized care and integrating it systematically with pharmacological therapy throughout the disease course, clinicians can address the pathophysiological synergy between inflammation, body composition, and metabolic homeostasis. This holistic, patient-centered approach has the potential not only to optimize treatment efficacy but also to improve long-term physical function, quality of life, and the likelihood of achieving durable, deep remission.

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Efficacy and Safety of Vedolizumab and Ustekinumab Treatment in Anti-TNF-Exposed Inflammatory Bowel Disease Patients

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Abstract

Objective: Patients with inflammatory bowel disease (IBD) who fail anti–tumor necrosis factor (anti-TNF) therapy require alternative biologics with different mechanisms of action. Vedolizumab (VDZ) and ustekinumab (UST) are established effective options. However, real-world comparative data remain limited.
Methods: We conducted a retrospective, single-center study of 114 anti-TNF-experienced IBD patients (40 ulcerative colitis [UC], 74 Crohn's disease [CD]) treated with VDZ or UST between 2017 and 2024. Clinical and laboratory parameters were collected at baseline, at 3 and 12 months, and at the last follow-up. Disease activity was assessed using the partial Mayo score (UC) and the Harvey–Bradshaw Index (CD). Treatment response, persistence, adverse events, and the need for surgery were analyzed.
Results: Of the 40 UC patients, 34 (85%) were treated with VDZ and 6 (15%) with UST. Among the 74 CD patients, 34 (46%) were treated with VDZ and 40 (54%) with UST. In UC, VDZ led to significant reductions in pMayo scores at 3 and 12 months ($p<0.0001$), whereas UST showed numerical improvement without statistical significance. In CD, both VDZ and UST significantly reduced HBI scores at 3 and 12 months ($p<0.001$). Treatment persistence did not differ significantly between VDZ and UST in the overall, UC, or CD cohorts. Adverse events occurred in 9 patients (7.9%), mostly mild, with no serious complications. Surgical interventions were required in 9 patients, most of whom were treated with VDZ.
Conclusion: Both agents were effective and safe in anti-TNF-experienced IBD patients. Our real-world data indicate distinct response patterns between UC and CD, underscoring the clinical utility of both agents as therapeutic options after anti-TNF failure.
Keywords: Clinical efficacy, Crohn's disease, safety profiles, ulcerative colitis, ustekinumab, vedolizumab.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, relapsing condition requiring long-term management.[1] The primary therapeutic goals are to suppress inflammation, achieve mucosal healing, and maintain long-term remission.[2-5] Primary and secondary nonresponse to anti–tumor necrosis factor (anti-TNF) agents has highlighted the need for novel biologic therapies with alternative mechanisms of action, such as vedolizumab (VDZ) and ustekinumab (UST).[6,7]

VDZ is a gut-selective IgG1 monoclonal antibody that binds to the α4β7 integrin, thereby inhibiting the migration of T lymphocytes from the circulation into the gastrointestinal mucosa.[8-10] UST is a fully human IgG1 monoclonal antibody that binds to the p40 subunit shared by interleukin-12 (IL-12) and interleukin-23 (IL-23), thereby preventing these cytokines from binding to their cell surface receptors and blocking downstream inflammatory signaling pathways. By inhibiting the IL-12/23 axis, UST suppresses both Th1- and Th17-mediated immune responses.[11]

VDZ and UST have been evaluated in numerous studies. Comparative studies have not demonstrated consistent superiority of one agent over the other, with both showing favorable efficacy profiles and low rates of adverse events. In a multicenter retrospective study, UST demonstrated similar efficacy when used as second- or third-line therapy, whereas VDZ was less effective as third-line treatment than when used as a second-line option.[12] Another large multicenter study in biologic-naïve patients with CD reported similar clinical response rates between VDZ and UST. However, mucosal healing was observed more frequently in the VDZ group, whereas treatment persistence was higher in the UST group. No significant differences were observed between the two groups regarding safety or the need for surgery.[13]

Compared with CD, fewer studies have assessed the comparative effectiveness of VDZ and UST in ulcerative colitis (UC). In a cohort from Japan, no significant differences were observed between the VDZ and UST groups in terms of remission and response rates. The safety profiles of both agents were similar, and no serious adverse events were reported.[14]

Multiple clinical studies have demonstrated that the safety profiles of UST and VDZ are comparable in both biologic-naïve patients and those with anti-TNF-refractory Crohn's disease.[11-18] Rates of serious adverse events and treatment-related complications were low and similar between the two therapies.[11,12,14,15] Furthermore, both agents were well tolerated in elderly patients, with comparable adverse event rates in these subgroups.[15,16]

In this study, we aimed to evaluate the effectiveness, treatment persistence, and safety of VDZ and UST in anti-TNF-experienced IBD patients in a real-world setting.

METHODS

We enrolled patients with IBD who received VDZ or UST after treatment with an anti-TNF agent in our IBD-specific gastroenterology outpatient clinic between 2017 and 2024. The diagnoses of UC and CD were established based on clinical, endoscopic, and histological findings in accordance with the guidelines current at the time of diagnosis. Patients who had completed the induction regimen of VDZ or UST with prior exposure to anti-TNF treatment were included in the study. Exclusion criteria were age <18 years, absence of prior anti-TNF exposure, failure to complete the induction regimen, or a diagnosis of indeterminate colitis.

Demographic variables (age, sex), clinical characteristics (diagnosis, disease activity, behavior, location/extent according to the Montreal classification[17]), endoscopic activity, biochemical parameters (leukocyte count, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], albumin), and adverse events were extracted from patient records and the hospital electronic database. Data were collected at baseline (initiation of VDZ or UST), at the 3rd month, 12th month, and the last follow-up visit.

The retrospective evaluation included adverse events, number of disease flares, new-onset complications, IBD-related surgery, and hospitalizations. Disease activity was assessed at the 3rd month, 12th month, and the last follow-up visit.

Disease activity was assessed using the Partial Mayo (pMayo) score for patients with UC and the Harvey–Bradshaw Index (HBI) for patients with CD at treatment initiation and during follow-up.

Treatment response was determined by changes in disease activity scores (pMayo and HBI) from baseline to the 3rd and 12th months. Clinical remission was defined using disease-specific indices: for UC, remission was defined as a pMayo score ≤2 with no individual subscore >1; for CD, remission was defined as an HBI ≤4, whereas clinical response was defined as a decrease of ≥3 points from baseline. In addition, treatment persistence and adverse events were retrospectively evaluated separately within each treatment group.

Statistical Analysis

Data were presented as mean±standard deviation (SD) or median (range), depending on the distribution characteristics of the variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were analyzed using either the independent-samples t test or the Mann–Whitney U test, depending on data distribution. These statistical methods were used to comprehensively evaluate relationships and differences between variable groups. Associations between variables and potential risk factors were analyzed using appropriate statistical techniques throughout the study period. A p value <0.05 was considered statistically significant.

Ethics Statement

This study was designed as a retrospective observational analysis. In accordance with national regulations and institutional policies, the requirement for written informed consent was waived by the local Institutional Review Board because of the retrospective nature of the study and the exclusive use of fully anonymized data. All patient information was obtained from electronic medical records and irreversibly anonymized before analysis; no identifiable personal data were accessed at any stage of the study. The study protocol was approved by Marmara University Faculty of Medicine, Non-Drug and Medical Device Research Ethics Committee (Approval Number: 09.2024.243, Date: 09.02.2024) and conducted in accordance with the Declaration of Helsinki.

RESULTS

Demographic and Clinical Characteristics

Overall Patient Group:

A total of 114 patients with a confirmed diagnosis of IBD were included in the study. The mean age of the patient group was 41.0±11.6 years, and the mean age at diagnosis was 29.0±9.9 years. Fifty-one (44.7%) were female and 63 (55.3%) were male (Table 1). In terms of diagnosis, 40 patients (35.1%) had UC and 74 (64.9%) had CD (Figure 1).

Ulcerative Colitis Subgroup:

Forty patients with a diagnosis of UC were included in the study. The mean age was 39.3±9.8 years, and the mean age at diagnosis was 27.9±8.8 years. Sixteen patients (40.0%) were female and 24 (60.0%) were male. Regarding disease extent, 11 patients (27.5%) had left-sided colitis, 7 (17.5%) had extensive colitis, and 22 (55.0%) had pancolitis (Table 1).

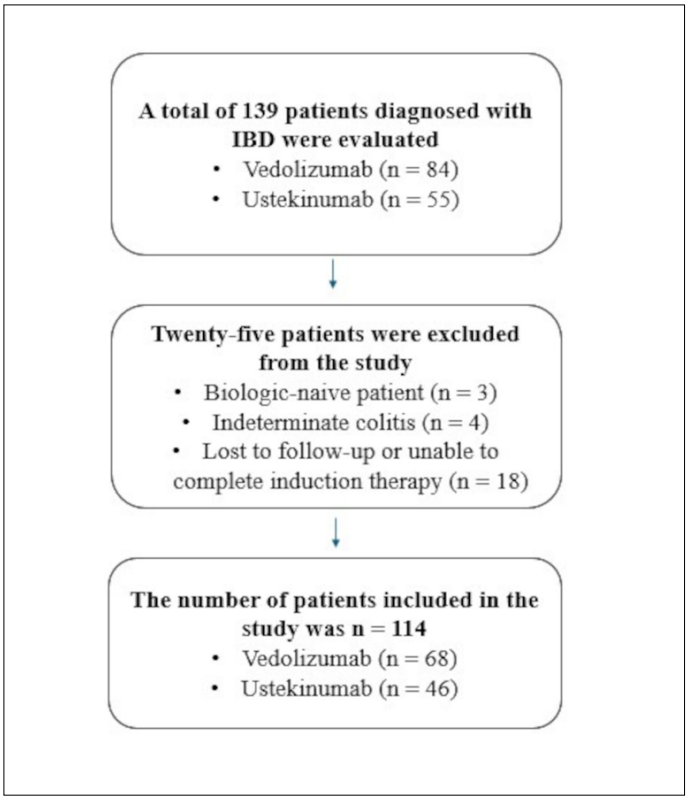


Figure 1. Flow diagram of the inclusion and exclusion of IBD patients treated with VDZ or UST.

Table 1. Patient demographics and clinical features

Characteristics	All Patients (N=114)	UC Subgroup (N=40)	CD Subgroup (N=74)
Age (years, mean ± SD)	41.0 ± 11.6	39.3 ± 9.8	42.0 ± 12.4
Age at diagnosis (years, mean ± SD)	29.0 ± 9.9	27.9 ± 8.8	29.6 ± 10.4
Female sex, n (%)	51 (44.7)	16 (40.0)	35 (47.3)
Male sex, n (%)	63 (55.3)	24 (60.0)	39 (52.7)
Left-sided colitis, n (%)	–	11(27.5)	–
Extensive colitis, n (%)	–	7(17.5)	–
Pancolitis, n (%)	–	22(55.0)	–
Age at diagnosis <16 years, n (%)	–	–	9 (12.2)
Age at diagnosis 17–40 years, n (%)	–	–	51 (68.9)
Age at diagnosis >40 years, n (%)	–	–	14 (18.9)
Ileal involvement, n (%)	–	–	10 (13.5)
Colonic involvement, n (%)	–	–	9 (12.2)
Ileocolonic involvement, n (%)	–	–	55 (74.3)
Inflammatory behavior, n (%)	–	–	5 (6.8)
Stricturing behavior, n (%)	–	–	14 (18.9)
Fistulizing behavior, n (%)	–	–	22 (29.7)
Both stricturing and fistulizing, n (%)	–	–	33 (44.6)
Presence of perianal fistula, n (%)	–	–	51 (68.9)
Presence of internal fistula, n (%)	–	–	24 (32.4)

SD :Standard deviation; UC : Ulcerative Colitis; CD : Crohn's Disease; (–) not.

Table 2. Treatment distribution and concomitant medication use in UC and CD patients

Characteristics	UC Patients (N = 40)	CD Patients (N = 74)
Vedolizumab (VDZ), n (%)	34 (85.0)	34 (45.9)
Ustekinumab (UST), n (%)	6 (15.0)	40 (54.1)
Oral mesalamine, n (%)	31 (77.5)	30 (40.5)
Azathioprine, n (%)	15 (37.5)	23 (31.1)

UC: Ulcerative Colitis; CD: Crohn's Disease; VDZ: Vedolizumab; UST: Ustekinumab. Concomitant medications refer to oral mesalamine or azathioprine used at the time of vedolizumab or ustekinumab initiation.

Crohn's Disease Subgroup:

Seventy-four patients with a diagnosis of CD were included in the study. The mean age was 42.0±12.4 years, and the mean age at diagnosis was 29.6±10.4 years. Of these, 35 (47.3%) were female and 39 (52.7%) were male. Analysis of age at diagnosis showed that 9 patients (12.2%) were diagnosed before the age of 16, 51 (68.9%) between 17 and 40 years, and 14 (18.9%) after 40 years (Table 1).

Ten patients (13.5%) had ileal involvement, 9 (12.2%) had colonic involvement, and 55 (74.3%) had ileocolonic involvement. Five patients (6.8%) had an inflammatory phenotype, 14 (18.9%) had a stricturing phenotype, 22 (29.7%) had a penetrating phenotype, and 33 (44.6%) had both stricturing and penetrating phenotypes. Stenosis was observed in 46 patients (62.2%), perianal fistula in 51 (68.9%), and internal fistulas in 24 (32.4%) (Table 1).

Among the UC patients, 34 (85%) were treated with VDZ and 6 (15%) with UST. Of these, 31 (77.5%) were using oral mesalamine concurrently, while 15 (37.5%) received concomitant azathioprine therapy (Table 2).

In the CD cohort, 34 (45.9%) were treated with VDZ and 40 (54.1%) with UST. Among them, 30 patients (40.5%) were using oral mesalamine and 23 (31.1%) were receiving concomitant azathioprine therapy (Table 2).

Vedolizumab dose intensification was administered in 3 UC patients (7.5%) and in 5 CD patients (6.8%). Three patients with Crohn's disease who were anti-TNF-naïve were excluded from the study.

Among the included patients, 78 (68.4%) had been exposed to a single anti-TNF agent, 33 (28.9%) to two anti-TNF agents, and 3 (2.6%) to three different anti-TNF agents (Table 3). When comparing the number of patients with prior exposure to a single versus multiple anti-TNF agents between the UST and VDZ groups, exposure to more than one anti-TNF agent was significantly higher in the UST group (p=0.013).

Among patients with UC, 5 (12.5%) had been exposed to more than one anti-TNF agent, compared with 31 (41.9%) of those with CD. This difference was also statistically significant (p=0.001).

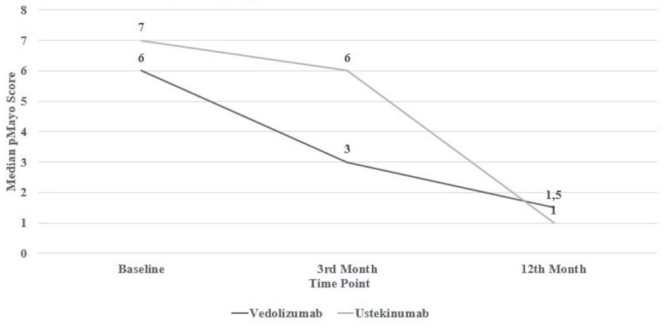
Assessment of Treatment Response

In UC patients treated with VDZ, the median pMayo score at treatment initiation was 6 (range: 0–9), which decreased to 3 (range: 0–8) at the 3rd month and further to 1.5 (range: 0–8) at the 12th month (Figure 2). A statistically significant reduction in pMayo scores was observed

Table 3. Number of biologic therapy exposures in study population

Single anti-TNF agent, n (%)	78 (68.4)
Two anti-TNF agents, n (%)	33 (28.9)
Three anti-TNF agents, n (%)	3 (2.6)

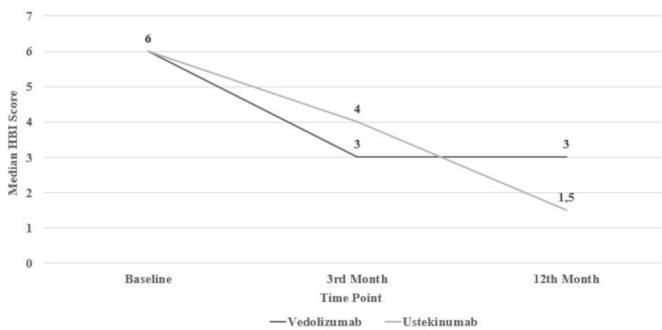
TNF: Tumor necrosis factor.



Time Point	VDZ Remission	UST Remission
3rd Month	14/34 (41.2%)	0/6 (0%)
12th Month	20/34 (58.8%)	3/6 (50.0%)

(Remission definitions: pMayo ≤2 for UC).

Figure 2. Median pMayo scores over time in UC patients treated with VDZ and UST.



Time Point	VDZ Remission	UST Remission
3rd Month	22/34 (64.7%)	24/40 (60.0%)
12th Month	22/34 (64.7%)	38/40 (95.0%)

(Remission definitions: HBI ≤4 for CD)

Figure 3. Median HBI scores over time in patients treated with VDZ and UST.

when baseline scores were compared with those at the 3rd and 12th months, respectively (p<0.0001 and p<0.0001).

In UC patients treated with UST, the median pMayo score was 7 (range: 5–9) at baseline, 6 (range: 6–6) at the 3rd month, and 1 (range: 1–6) at the 12th month. Although pMayo scores decreased from baseline to the 3rd and 12th months, these reductions were not statistically significant (p=0.15 and p=0.06, respectively) (Figure 2).

Among UC patients, no statistically significant difference was observed in baseline pMayo scores between the VDZ and UST groups (p=0.17). In both treatment groups, pMayo scores decreased significantly from pretreatment to the 3rd month and from pretreatment to the 12th month (p<0.0001 and p<0.0001) (Figure 2).

In CD patients treated with VDZ, the median HBI score at baseline was 6 (range: 1–17), decreasing to 3 (range: 0–15) at the 3rd month and remaining 3 (range: 0–12) at the 12th month. Comparisons of baseline HBI scores with those at the 3rd and 12th months showed statistically significant reductions (p<0.0001 and p=0.001, respectively) (Figure 3). In CD patients treated with UST, the median HBI score was 6 (range: 0–19) at baseline, 4 (range: 0–18) at the 3rd month, and 1.5 (range: 0–10) at the 12th month. Significant reductions in HBI scores were observed from baseline to the 3rd month and from baseline to the 12th month (p<0.0001 for both comparisons) (Figure 3). No statistically significant difference in baseline HBI scores was observed between the VDZ and UST groups (p=0.95), indicating comparable baseline disease activity.

A significant decline in ESR was observed at weeks 26 and 52, and CRP levels showed a significant reduction at week 52 in both the vedolizumab and ustekinumab groups (Supplementary Table 1).

Treatment Persistence

No significant difference in treatment response was observed between patients who received VDZ and those who received UST in the overall cohort or in the UC and CD subgroups (p=0.51, p=0.69, and p=0.36, respectively) (Figure 4).

Treatment Discontinuation

Treatment with VDZ or UST was discontinued in 40 patients. Of these, 15 patients (37.5%) had UC and 25 patients (62.5%) had CD. Among those who discontinued treatment, 9 patients (22.5%) had been receiving UST and 31 patients (77.5%) had been receiving VDZ.

Reasons for Treatment Discontinuation

In our study, 4 patients chose not to continue treatment, and therapy was discontinued. One patient was lost to follow-up during the COVID-19

Supplementary Table 1. Changes in laboratory parameters according to treatment group

Parameter	Treatment	Baseline (Median)	Week 6 (Median)	p	Week 14 (Median)	p	Week 26 (Median)	p	Week 52 (Median)	p
WBC (×10³/μL)	VDZ	9450	7700	0.80	7440	0.36	7350	0.16	7575	0.21
	UST	9610	8640	0.75	8140	0.40	8150	0.31	8580	0.22
CRP (mg/L)	VDZ	25.7	18.3	0.19	17.4	0.40	16.5	0.10	17.6	0.02
	UST	29.0	14.5	0.12	12.8	0.07	14.1	0.09	17.4	0.04
ESR (mm/h)	VDZ	25.2	22.7	0.62	20.5	0.02	21.5	0.053	20.7	0.003
	UST	44.9	29.6	0.50	27.8	0.04	28.3	0.03	15.4	0.01

WBC: White blood cell; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; VDZ: Vedolizumab; UST: Ustekinumab. Values are expressed as medians due to non-normal data distribution. p-values indicate within-group comparisons versus baseline (Wilcoxon signed-rank test). Statistical significance was defined as p < 0.05.

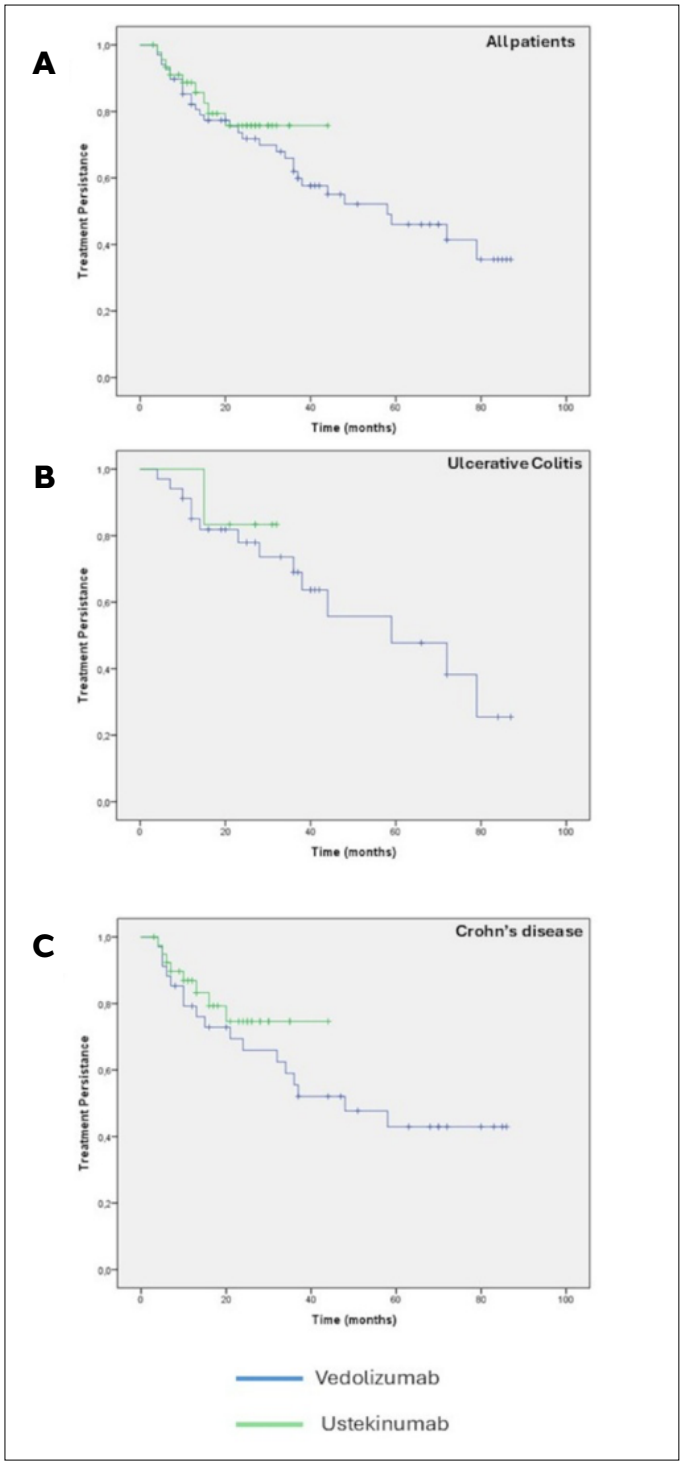


Figure 4. Comparison of treatment persistence between VDZ and UST.

pandemic and discontinued treatment. In 7 patients, treatment was discontinued due to adverse events, including arthritis (n=3), dyspnea (n=1), hypoglycemia (n=1), weight loss (n=1), and scalp rash (n=1).

Evaluation of Treatment Nonresponse

Primary nonresponse (lack of clinical improvement during the induction phase) was observed in 9 patients, whereas secondary loss of response (loss of clinical efficacy during the maintenance phase after initial improvement) occurred in 19 patients (Figure 5).

Adverse Reactions and Surgery

A total of 9 patients experienced treatment-related adverse events. In the UST group, 1 patient developed vertigo following the loading dose and another developed arthritis. In the VDZ group, adverse events were reported in 7 patients, including exertional dyspnea, hypoglycemic episodes, weight loss, scalp rash, arthritis, and cutaneous rashes.

Nine patients required surgical intervention. Among them, 3 underwent right hemicolectomy; all had CD and were receiving vedolizumab therapy. In one case, surgery was performed due to primary nonresponse, in another due to secondary loss of response, and in the third case treatment was continued postoperatively after remission was achieved.
One CD patient receiving VDZ underwent subtotal colectomy due to secondary loss of response, resulting in treatment discontinuation. Another patient with UC receiving VDZ underwent total proctocolectomy due to primary nonresponse, and treatment was discontinued accordingly. Additionally, abscess drainage procedures were performed in 4 patients due to perianal or intra-abdominal abscesses (Table 4).

DISCUSSION

In this study, real-world data on VDZ and UST treatments were compared in 114 patients with IBD who were unresponsive to at least one anti-TNF agent. The therapeutic efficacy and safety of both biologic agents were assessed by recording clinical response, treatment discontinuation rates, adverse event profiles, and safety outcomes during induction and maintenance therapy.

In UC patients, VDZ achieved statistically significant clinical remission in both the induction and maintenance phases, as measured by the pMayo score. In contrast, UST was associated with a numerical reduction in the pMayo score that did not reach statistical significance. Among CD patients, both the UST and VDZ treatment groups achieved statistically significant clinical remission during the induction and maintenance phases, as measured by the HBI. Numerical improvement in HBI scores was observed in both groups during induction, whereas a more pronounced numerical reduction was noted in UST-treated patients compared with those receiving VDZ during maintenance therapy. No statistically significant difference in treatment persistence was observed between the two agents, either in the overall IBD cohort or within the UC and CD subgroups. Both treatments were safe, with similar adverse event and safety profiles.

VDZ induced clinical remission in 42% of UC patients at the 3rd month and 60% at the 12th month, closely resembling the results of the GEMINI I trial.[8] In the UST-treated UC group, no clinical remission was observed at the 3rd month, whereas 60% of patients achieved clinical remission at the 12th month. The results in this cohort were not statistically significant; however, they were consistent with published data. In the UNIFI trial, clinical remission rates were relatively low during the induction phase (15.6% at week 8) but more than doubled during the maintenance phase, reaching 43.8% at week 44.[18] Similar to the UNIFI trial, our study demonstrated a marked increase in remission rates during the maintenance phase among patients treated with UST, with 60% achieving remission at the 12th month. The slightly higher remission rate observed in our cohort compared with UNIFI may be attributable to differences in patient characteristics and study design. While UNIFI was a phase 3 randomized controlled trial evaluating the efficacy of UST in a heterogeneous UC population under strict protocol-defined remission criteria, our study represents real-world data, potentially involving a more selected patient population and a less rigid definition of remission.[18]

Table 4. Surgical outcomes and indications in patients under biologic treatment

Surgical Procedure	Number of Patients	Diagnosis	Biologic Agent	Reason for Surgery / Outcome
Right Hemicolectomy	3	CD	VDZ	1 primary NR*, 1 secondary NR*, 1 continued post-op due to remission
Subtotal Colectomy	1	CD	VDZ	Secondary NR*, treatment discontinued
Total Proctocolectomy	1	UC	VDZ	Primary NR*, treatment discontinued
Intraabdominal Abscess Drainage	4	CD and UC	VDZ	Perianal or intra-abdominal abscess

NR: Non-response; CD: Crohn's disease; UC: Ulcerative colitis; VDZ: Vedolizumab; UST: Ustekinumab.

Another important consideration is that the number of UC patients receiving UST in our study was relatively low (n=6). This disproportionality in patient numbers represents a limitation in comparing response among UC patients. The apparent delay in short-term clinical improvement should therefore be interpreted cautiously. Furthermore, the rate of multiple anti-TNF resistance was higher in this group; only 5% (n=2) of patients in the VDZ group had failed more than one anti-TNF agent, compared with 50% (n=3) in the UST group.

Several studies have included anti-TNF-naïve patients in comparative analyses. In one study involving 106 UC patients (64 treated with VDZ and 42 with UST) who were either anti-TNF-naïve or experienced, no significant differences were observed between the two treatments in terms of remission and response rates at weeks 6, 22, and 54. The Clinical Activity Index (CAI) was used to assess disease activity in that study.[14] Another study using the same remission index as our study (pMayo ≤2) reported no significant differences in clinical remission at weeks 14 and 52.[19]

In our CD cohort, VDZ induced remission in 65% at the 3rd month and 66% at the 12th month, whereas the corresponding rates for UST were 60% and 95%, respectively. These findings are consistent with previous studies.[20-25] Multiple studies in anti-TNF-experienced CD populations have shown that UST may be more effective than VDZ during the maintenance phase. However, studies in anti-TNF-naïve populations yielded mixed results, with some showing similar outcomes and others demonstrating differences.[13,26,27] Another study including anti-TNF-experienced CD patients demonstrated that the superiority of UST over VDZ was particularly evident in patients with ileal involvement and penetrating disease behavior.[28] A prospective study reported that, in anti-TNF-experienced CD patients, both clinical remission (HBI ≤4) and biochemical remission (CRP ≤5 mg/L and fecal calprotectin ≤250 µg/g) rates at week 52 were significantly higher in the UST group.[24] Long disease duration and the presence of perianal disease have generally been associated with poorer outcomes for VDZ. In contrast, ileocolonic disease has been linked to higher remission rates in response to UST.[22,29]

In most comparable studies conducted in UC patients, treatment persistence rates were similar to those observed in our study, with no significant differences between the two agents.[19,30] Some studies in CD patients reported comparable outcomes at week 52, whereas others demonstrated higher long-term treatment persistence with UST.[13,21-23,29,31,32]

No serious adverse events were observed with either biologic agent in our study. Most studies conducted in patients with IBD have demonstrated comparable safety profiles for both agents, and our findings support this evidence.[13,24,27,29,33]

Overall, both VDZ and UST appear to be well tolerated across a wide

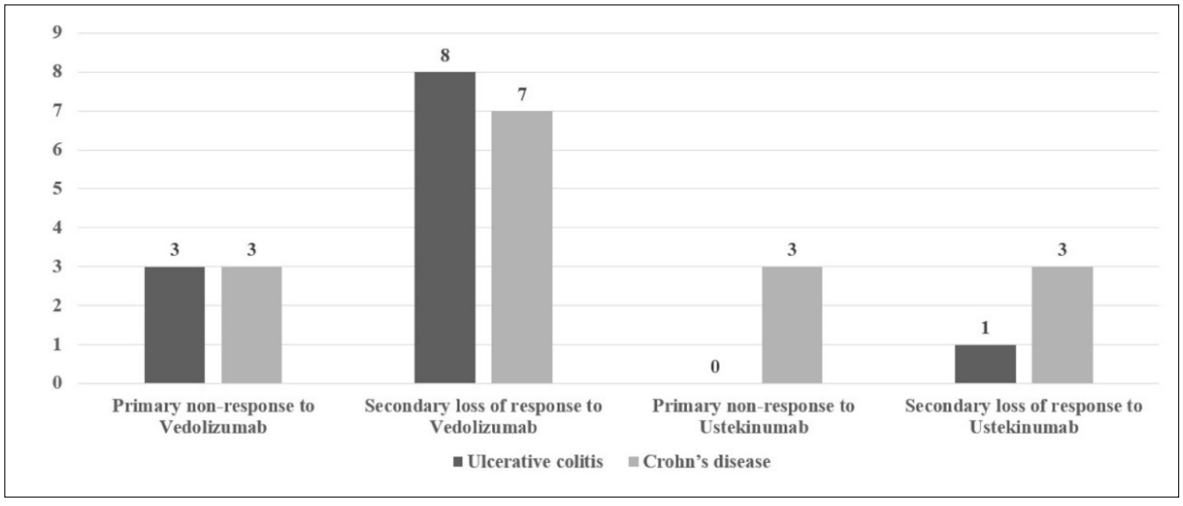


Figure 5. Patients with primary or secondary nonresponse to vedolizumab or ustekinumab.

range of patients, including older adults. In our study, 10 patients aged ≥60 years (1 with UC, 9 with CD) received biologic therapy (4 with UST and 6 with VDZ), with no serious complications or infections reported in this subgroup. These findings support the safety of both agents in elderly patients and are consistent with published evidence.[15,16,34]

A major strength of this study is its focus on real-world data evaluating the effectiveness of VDZ and UST as second- or third-line therapies in anti-TNF-experienced patients. The tertiary-center setting and access to a broad, diverse patient population further enhance the study's clinical relevance.

This study has several limitations. The retrospective, single-center design inherently limits the generalizability of the findings. In addition, the imbalance in sample sizes between the treatment groups and the overall small cohort size precluded a robust head-to-head comparative analysis. Another important limitation was the lack of adequate endoscopic and biochemical follow-up data at both 3 and 12 months, which prevented evaluation of mucosal healing and the use of a modified Mayo endoscopic subscore. The absence of fecal calprotectin evaluation during follow-up is another limitation.

Given these limitations, the primary focus of this study was not a direct comparison between VDZ and UST but rather an evaluation of their individual effectiveness, treatment persistence, and safety profiles in a real-world cohort. Future prospective, multicenter studies with standardized endoscopic and biochemical monitoring and larger sample sizes are needed to validate these findings. This study demonstrates that both UST and VDZ are effective in achieving clinical remission in anti-TNF-refractory IBD patients. High clinical success rates can be achieved with appropriate patient selection. Therefore, VDZ and UST represent effective and safe therapeutic options for achieving sustained, long-term disease control in patients with UC or CD who have failed anti-TNF therapy.

Ethics Committee Approval: The study's protocol received approval from the Ethical Committee for Clinical Investigations of the Marmara University Faculty of Medicine, Non-Drug and Medical Device Research Hospital (Approval Number: 09.2024.243, Date: 09.02.2024).

Informed Consent: Informed consent was waived by the local Clinical Research Ethics Committee due to the retrospective nature of the study and the use of anonymized patient data.

Conflict of Interest: Haluk Tarik Kani has been speaker or advisor for Abbvie, Janssen, Sanofi, Takeda and Ferring. The remaining authors declare no conflicts of interest.

Peer-review: Externally peer-reviewed.

Author Contribution: Concept – N.N., H.T.K.; Design – N.N., H.T.K.; Supervision – Y.Ö.A., Ö.A.; Data Collection and/or Processing - N.N., H.T.K.; Analysis and/or Interpretation - N.N., H.T.K.; Literature Review – N.N., T.T., H.T.K.; Writing – N.N., T.T.; Critical Review – Y.Ö.A., Ö.A., H.T.K.

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Treatment Strategy as a Determinant of Carbon Footprint in Inflammatory Bowel Disease Care

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Abstract

Objective: The environmental footprint of healthcare is increasingly recognized as a component of care quality; however, patient-level carbon emissions associated with inflammatory bowel disease (IBD) remain insufficiently quantified. This study aimed to prospectively quantify the carbon footprint of IBD care and compare it across maintenance treatment strategies.

Methods: This prospective observational cohort study was conducted at a tertiary IBD referral center between December 2025 and January 2026. Consecutive adults with ulcerative colitis or Crohn's disease were included. The annual carbon footprint (kg carbon dioxide equivalent [CO_2e] per patient-year) was estimated using activity-based accounting across patient travel, clinical care delivery, and pharmaceuticals. Patients were stratified by dominant maintenance therapy. Independent predictors were assessed using multivariable linear regression.

Results: Among 248 patients (169 with ulcerative colitis and 79 with Crohn's disease), the median annual carbon footprint was 52.6 kg CO_2e (interquartile range, 31.8–74.2). Patient travel accounted for 46.2% of emissions, followed by pharmaceuticals (29.4%) and clinical care delivery (24.4%). The carbon footprint was highest with intravenous biologics (86.1 kg CO_2e), followed by subcutaneous biologics (48.9 kg CO_2e) and oral/systemic therapy (24.7 kg CO_2e) ($P < .001$). In adjusted analyses, intravenous and subcutaneous biologics were associated with increases of 31.4 kg CO_2e (95% CI, 24.1–38.7) and 18.6 kg CO_2e (95% CI, 12.2–25.1), respectively. Each 10-km increase in one-way travel distance was associated with an additional 3.2 kg CO_2e (95% CI, 1.9–4.5).

Conclusion: Long-term IBD management is associated with a measurable carbon footprint, primarily driven by treatment modality and patient travel. A more sustainable organization of care may reduce the environmental impact while preserving care standards.

Keywords: Carbon footprint, Crohn's disease, health care delivery, inflammatory bowel diseases, ulcerative colitis.

INTRODUCTION

Climate change is increasingly recognized as a determinant of population health, and the environmental performance of healthcare systems has become a measurable component of responsible clinical practice.[1] Healthcare delivery accounts for a substantial share of global greenhouse gas emissions, prompting renewed attention to sustainability within routine care. Chronic diseases that require long-term, resource-intensive management warrant particular scrutiny in this context.

Inflammatory bowel diseases (IBD), which primarily include ulcerative colitis (UC) and Crohn's disease (CD), are chronic conditions that exemplify the need for long-term, resource-intensive care. The global burden of IBD continues to rise, with increasing incidence in newly industrialized regions and sustained prevalence in established Western populations.[2,3] Because disease onset typically occurs in early adulthood and IBD follows a relapsing-remitting course, patients often require decades of structured monitoring, repeated objective assessments of inflammation, and prolonged pharmacologic therapy. Over time, even modest differences in care intensity may result in significant cumulative environmental impact.

Recent discussions have introduced the concept of sustainable or "green" IBD management, suggesting that environmental considerations should complement clinical effectiveness and safety in the design of care pathways.[4] Contemporary treat-to-target strategies, formalized in STRIDE-II, prioritize objective disease control and tight monitoring to prevent structural damage and long-term complications.[5] Although these approaches have improved clinical outcomes, they may also increase healthcare utilization through more frequent outpatient visits, laboratory testing, imaging, endoscopy, and administration of advanced therapies. The environmental implications of these intensified care models remain insufficiently quantified.

While the environmental determinants of IBD risk and activity have been extensively characterized,[6,7] the environmental impact of delivering IBD care has received far less attention. In particular, prospective patient-level comparisons of carbon footprints across maintenance treatment

MAIN POINTS

- The median annual carbon footprint of inflammatory bowel disease (IBD) care was 52.6 kg CO_2e per patient-year in this prospective cohort.
- Patient travel was the largest contributor to total emissions (46.2%), followed by pharmaceuticals (29.4%) and clinical care delivery (24.4%).
- Treatment modality was the strongest independent predictor of carbon footprint, with intravenous biologics associated with the highest emissions.
- Disease activity was not independently associated with the carbon footprint after multivariable adjustment.
- Longer travel distances and a higher number of in-person healthcare encounters were independently associated with increased emissions.

modalities—oral therapies, self-administered subcutaneous biologics, and hospital-based intravenous biologics—using standardized carbon accounting methods are limited.

We hypothesized that treatment modality independently influences the annual per-patient carbon footprint of IBD care, with hospital-based intravenous therapies generating higher emissions than oral or subcutaneous regimens.

To address this gap, we conducted a prospective observational study at a tertiary IBD referral center. Using a standardized activity-based carbon accounting methodology, we aimed to: (i) quantify annual per-patient carbon dioxide equivalent (CO_2e) emissions, (ii) identify dominant emission sources within the care pathway, and (iii) compare carbon footprints across major maintenance treatment strategies in a real-world tertiary-care setting.

METHODS

Study Design and Setting

This prospective observational cohort study was conducted at a high-volume tertiary inflammatory bowel disease (IBD) referral center. The protocol was developed in accordance with the Declaration of Helsinki, and the study was designed and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[8]

Patients were enrolled between December 2025 and January 2026. For each participant, the carbon footprint was calculated for the preceding 12-month observation period.

Participants and Eligibility Criteria

Adults aged ≥18 years with an established diagnosis of ulcerative colitis (UC) or Crohn's disease (CD), confirmed by standard clinical, endoscopic, histopathological, and/or radiological criteria, and under active follow-up at the study center were eligible.

Exclusion criteria included inability or unwillingness to provide written informed consent, incomplete medical records that prevented accurate extraction of data for the preceding 12-month period, receipt of primary IBD care at another institution, or concomitant primary immunodeficiency or chronic infectious colitis.

No exclusions were made based on disease activity, phenotype, disease duration, or treatment type, in order to reflect routine clinical practice.

Data Collection

Data were collected using a structured and piloted case report form. Clinical and healthcare utilization data were extracted from the hospital's electronic medical record system. Travel-related variables, including mode of transportation and caregiver accompaniment, were verified through brief structured interviews at enrollment when not available in the electronic records.

Recorded variables included demographic and clinical characteristics (age, sex, disease subtype, disease duration, prior surgery, and disease activity indices [partial Mayo score for UC; Harvey–Bradshaw Index for CD]), treatment details (all IBD-related medications, specific agents, dose, route of administration, and dosing frequency), healthcare utilization (number and type of outpatient visits, infusion sessions, endoscopic procedures, and imaging studies during the 12-month period), and travel patterns (round-trip distance, primary mode of transportation, and visit frequency).

Carbon Footprint: Definition and System Boundaries

The primary outcome was the annual patient-level carbon footprint of IBD care, expressed as kilograms of carbon dioxide equivalent per patient-year (kg CO_2e per patient-year).

A healthcare-delivery–focused system boundary was adopted, consistent with the Greenhouse Gas Protocol and established healthcare carbon accounting frameworks.[9] The analysis included direct and upstream emissions (Scope 1, Scope 2, and selected patient-attributable Scope 3 emissions, including pharmaceutical production and medical consumable manufacturing) associated with discrete care activities.

Emissions related to hospital infrastructure, capital equipment, staff commuting, and non-allocable waste streams were excluded because reliable patient-level attribution was not feasible.

Three emission domains were evaluated: patient travel, clinical care delivery, and pharmaceuticals.

Carbon Footprint Calculation

Carbon footprint estimation followed an activity-based accounting approach aligned with ISO 14040/44 life cycle assessment principles.[10]

Travel Emissions

Travel emissions were calculated by multiplying round-trip travel distance (km) by transport-specific emission factors (kg CO_2e/km). Standard emission factors for private car travel were applied when no alternative mode was reported.

For patients aged ≥65 years or those reporting functional limitations requiring assistance, emissions for one accompanying caregiver were included. A sensitivity analysis excluding caregiver travel was also performed.

Clinical Care Delivery Emissions

Per-event emission factors were assigned to outpatient visits, infusion sessions, and endoscopic procedures based on published life cycle assessment literature evaluating comparable healthcare services.[11] Reported estimates for in-person outpatient visits vary depending on system boundaries and service intensity; emission factors were selected from tertiary-care settings with comparable structures and applied uniformly across patients. Only activity-specific emissions were included

to avoid overlap with pharmaceutical or travel emissions.

Pharmaceutical Emissions

Pharmaceutical emissions were calculated using medication-specific cradle-to-gate emission factors (kg CO_2e per dose or per milligram) identified from peer-reviewed life cycle assessment literature where available.[12]

For medications without published emission data, proxy emission factors were estimated using therapeutically comparable agents with available cradle-to-gate data. Emissions were adjusted proportionally based on the annual cumulative dose and relative molecular weight between the index medication and the reference agent. Annual pharmaceutical emissions were calculated by multiplying the cumulative annual dose by the emission factor per unit.

To prevent double counting, pharmaceutical emission factors were restricted to production-related emissions and excluded transport or facility components already accounted for in other domains. All emission factors and formulas were prespecified prior to analysis and applied consistently.

Exposure Groups

Patients were classified into three mutually exclusive groups based on the dominant maintenance therapy during the 12-month period: oral/systemic agents, subcutaneous biologics, and intravenous biologics. A predefined hierarchical approach was applied, with intravenous biologics taking precedence over subcutaneous biologics, and subcutaneous biologics over oral/systemic agents.

Outcome Measures

The primary outcome was the total annual IBD-related carbon footprint (kg CO_2e per patient-year).

Secondary outcomes included the absolute and proportional contributions of each emission domain and the comparison of total carbon footprints across treatment groups.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are presented as number (percentage).

Between-group comparisons were performed using analysis of variance (ANOVA) or the Kruskal–Wallis test for continuous variables, and the chi-square or Fisher's exact test for categorical variables.

Independent predictors of carbon footprint were assessed using multivariable linear regression, including prespecified covariates: treatment group (oral/systemic agents as the reference), age, disease subtype, disease activity index, and one-way travel distance.

Multicollinearity was evaluated using variance inflation factors (VIF), with values <5 considered acceptable. Model assumptions were assessed by inspection of residual plots and evaluation of normality diagnostics.

Regression results are reported as β coefficients with 95% confidence intervals (CI). A two-sided $P < .05$ was considered statistically significant. P values are reported according to AMA guidelines.

All analyses were performed using R statistical software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria).

Because prior prospective data on patient-level carbon footprint in IBD care were unavailable, a formal sample size calculation was not feasible. Therefore, all consecutive eligible patients during the predefined study period were enrolled.

Ethical Considerations

The study protocol was approved by the Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (Approval Number: 677, Date: 02.12.2025) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

RESULTS

Patient Characteristics

A total of 248 consecutive patients with inflammatory bowel disease (IBD) were included: 169 (68.1%) with ulcerative colitis (UC) and 79 (31.9%) with Crohn's disease (CD). Baseline characteristics are presented in Table 1.

The median age was 42 years (interquartile range [IQR], 34–51), and 136 patients (54.8%) were male. The median disease duration was 6.4 years (IQR, 3.1–11.2), which was significantly longer among patients

Table 1. Baseline characteristics of the study cohort (N = 248)

Characteristic	Total Cohort (n = 248)	Ulcerative Colitis (n = 169)	Crohn's Disease (n = 79)	P
Age, years, median (IQR)	42 (34–51)	43 (35–52)	40 (32–49)	.15
Male sex, n (%)	136 (54.8)	89 (52.7)	47 (59.5)	.38
Disease duration, years, median (IQR)	6.4 (3.1–11.2)	5.8 (2.8–10.1)	7.1 (4.2–12.9)	.041
IBD-related surgery, n (%)	37 (14.9)	14 (8.3)	23 (29.1)	< .001
Primary treatment strategy, n (%)				< .001
Oral/systemic	152 (61.3)	121 (71.6)	31 (39.2)	
Subcutaneous biologic	58 (23.4)	35 (20.7)	23 (29.1)	
Intravenous biologic	38 (15.3)	13 (7.7)	25 (31.6)	
Biologic therapy (any), n (%)	96 (38.7)	48 (28.4)	48 (60.8)	< .001

IBD indicates inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IQR, interquartile range. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. P values for primary treatment strategy reflect overall group comparison.

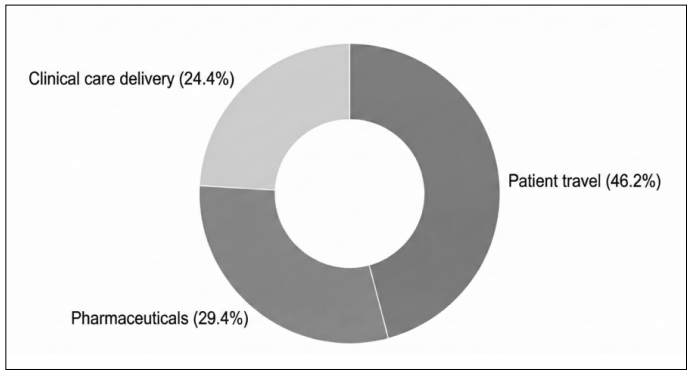

Figure 1. Proportional contribution of emission domains to the annual carbon footprint of IBD care (N = 248).
Patient travel accounted for 46.2% of total emissions, followed by pharmaceuticals (29.4%) and clinical care delivery (24.4%). The proportions represent the relative contribution of each emission domain to the cohort's median annual carbon footprint (kg CO_2e per patient-year). IBD indicates inflammatory bowel disease; CO_2e, carbon dioxide equivalent.

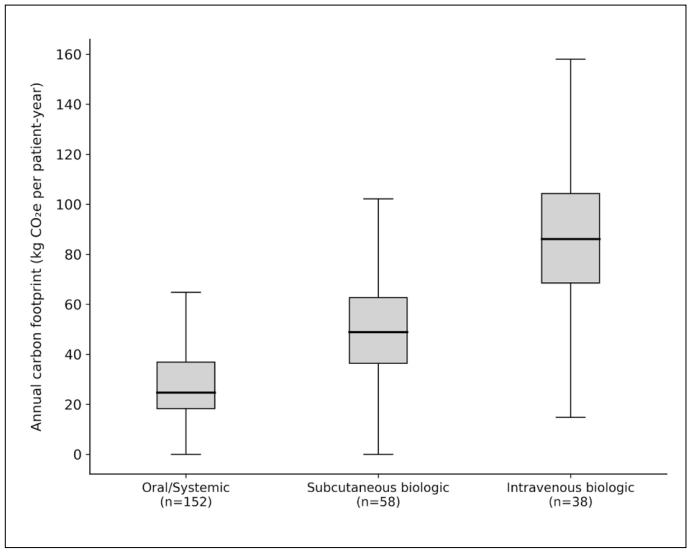

Figure 2. Annual carbon footprint according to maintenance treatment strategy. Boxplots show the distribution of annual carbon footprint (kg CO_2e per patient-year) across oral/systemic agents, subcutaneous biologics, and intravenous biologics. The central line represents the median; boxes indicate the interquartile range (IQR); whiskers extend to 1.5 × IQR. Overall differences were assessed using the Kruskal–Wallis test (P < .001). Post hoc Dunn's test demonstrated significant differences for all pairwise comparisons (all P < .001).

with CD than among those with UC (7.1 vs 5.8 years; P = .041). A history of IBD-related surgery was more prevalent in the CD group (29.1% vs 8.3%; P < .001).

Overall, 96 patients (38.7%) received biologic therapy, including 58 (23.4%) receiving subcutaneous agents and 38 (15.3%) receiving intravenous agents. Biologic therapy was more common among patients with CD than among those with UC (60.8% vs 28.4%; P < .001).

Overall Carbon Footprint of IBD Care

The median annual carbon footprint of IBD care was 52.6 kg carbon dioxide equivalent (CO_2e) per patient-year (IQR, 31.8–74.2).
Patient travel was the dominant emission source, accounting for 46.2% of total emissions, followed by pharmaceuticals (29.4%) and clinical care delivery (24.4%) (Figure 1).

Carbon Footprint by Treatment Strategy

Annual carbon footprint differed significantly across the three maintenance treatment strategies (Kruskal–Wallis test; P < .001) (Figure 2).
Patients receiving oral/systemic therapy had the lowest median footprint (24.7 kg CO_2e per patient-year; IQR, 18.3–36.9). Those receiving subcutaneous biologics had a higher median footprint (48.9 kg CO_2e; IQR, 36.4–62.7; P < .001 vs oral/systemic therapy). The highest emissions were observed in the intravenous biologics group (86.1 kg CO_2e; IQR, 68.5–104.3), which was significantly higher than those in both other groups (both P < .001).

Contribution of Emission Domains by Treatment

The proportional contribution of each emission domain varied according to treatment modality (Table 2).

In the intravenous biologics group, patient travel accounted for the largest share (52.8%), followed by pharmaceuticals (27.6%) and clinical care delivery (19.6%).

Among patients receiving subcutaneous biologics, pharmaceuticals were the dominant contributor (41.3%), with travel and clinical care delivery accounting for 34.7% and 24.0%, respectively.
In the oral/systemic group, emissions were more evenly distributed, with clinical care delivery representing 38.9%, travel 36.5%, and pharmaceuticals 24.6%.

Disease Subtype Analysis

At the cohort level, patients with CD had a higher median carbon foot-

Table 2. Annual carbon footprint by emission domain and treatment strategy

Treatment Strategy	n	Total Footprint, kg CO_2 e per Patient-Year, Median (IQR)	Patient Travel, Median kg (% of total)	Pharmaceuticals, Median kg (% of total)	Clinical Care Delivery, Median kg (% of total)
Oral/systemic agents	152	24.7 (18.3–36.9)	9.0 (36.5)	6.1 (24.6)	9.6 (38.9)
Subcutaneous biologics	58	48.9 (36.4–62.7)	17.0 (34.7)	20.2 (41.3)	11.7 (24.0)
Intravenous biologics	38	86.1 (68.5–104.3)	45.5 (52.8)	23.8 (27.6)	16.9 (19.6)
Total	248	52.6 (31.8–74.2)	24.3 (46.2)	15.5 (29.4)	12.8 (24.4)

CO_2e indicates carbon dioxide equivalent; IQR, interquartile range. Values are presented as the median (IQR) for total annual carbon footprint and the median absolute contribution of each emission domain. Percentages represent the proportional contribution to total emissions. Percentages may not sum to 100 due to rounding.

Table 3. Multivariable linear regression of annual carbon footprint

Predictor	Adjusted β (kg CO_2e per Patient-Year)	95% CI	P
Treatment strategy			
Subcutaneous biologic	18.6	12.2–25.1	< .001
Intravenous biologic	31.4	24.1–38.7	< .001
Travel distance (per 10-km increase)	3.2	1.9–4.5	< .001
Healthcare encounters (per additional encounter per year)	1.1	0.3–1.9	.008
Disease subtype (CD vs UC)	2.8	−3.1–8.7	.35
Age (per 10-year increase)	−0.5	−2.1–1.1	.54
Disease activity index	0.7	−0.5–1.9	.24

Reference category for treatment strategy: oral/systemic agents. β indicates regression coefficient; CI, confidence interval; CO_2e, carbon dioxide equivalent; UC, ulcerative colitis; CD, Crohn's disease. Model $R^2 = 0.62$. β coefficients represent adjusted changes in annual carbon footprint (kg CO_2e per patient-year).

print than those with UC (61.9 vs 46.8 kg CO_2e; P = .002). However, this association was no longer significant after multivariable adjustment for treatment strategy, suggesting that the unadjusted difference was largely explained by differences in treatment strategy rather than disease subtype alone.

Predictors of Carbon Footprint

Multivariable linear regression identified treatment modality as the strongest independent predictor of the annual carbon footprint (Table 3). The final model explained 62% of the variance ($R^2 = 0.62$).

Compared with oral/systemic therapy, intravenous biologics were associated with an adjusted increase of 31.4 kg CO_2e per patient-year (95% CI, 24.1–38.7; P < .001), and subcutaneous biologics with an increase of 18.6 kg CO_2e per patient-year (95% CI, 12.2–25.1; P < .001).

Each 10-km increase in one-way travel distance was independently associated with an additional 3.2 kg CO_2e annually (95% CI, 1.9–4.5; P < .001).

The total number of in-person healthcare encounters was also independently associated with higher emissions (β = 1.1 kg CO_2e per additional encounter per year; 95% CI, 0.3–1.9; P = .008).

Disease subtype, age, and disease activity indices were not independently associated with carbon footprint after multivariable adjustment.

DISCUSSION

In this prospective cohort study, we quantified the patient-level carbon footprint associated with long-term inflammatory bowel disease (IBD) management. Our findings demonstrate substantial variability in emissions. This variability appears to be driven primarily by treatment modality and patterns of healthcare utilization, rather than by the intrinsic clinical characteristics of the disease.

The median annual carbon footprint of 52.6 kg CO_2e per patient indicates that chronic IBD care is associated with a measurable environmental burden. Consistent with broader healthcare analyses,[1,9] patient travel was the largest contributor, accounting for nearly half of total emissions. Treatment modality was the strongest predictor in the adjusted model, with intravenous biologics associated with the highest carbon footprint, followed by subcutaneous biologics and oral/systemic therapies.

After multivariable adjustment, disease activity indices were not independently associated with emissions. This finding suggests that the environmental impact reflects structural and organizational features of care delivery more than clinical disease severity. In addition to structural determinants, patient-level lifestyle and psychosocial factors may also influence healthcare utilization patterns in IBD.[13] These data indicate that sustainability considerations can be incorporated into care models without compromising established monitoring and treatment standards.

The higher footprint observed with intravenous biologics appears to be attributable to recurrent hospital-based infusion visits and upstream emissions related to pharmaceutical manufacturing.[12] While biologic therapies remain essential for moderate-to-severe IBD, the use of subcutaneous formulations, when clinically appropriate, may reduce travel-related and facility-associated emissions. Integrating environmental considerations into health technology assessment frameworks may further contextualize the carbon impact of therapeutic strategies.[14]

Across treatment groups, travel-related emissions represented the largest potentially modifiable component of the overall footprint. Telemedicine has been shown to reduce healthcare-associated emissions without adversely affecting patient satisfaction or quality of care.[15] Practical approaches may include structured telehealth follow-up for stable patients, consolidation of laboratory testing with clinic visits, and optimization of follow-up intervals.

Diagnostic and monitoring procedures also contribute to the environmental burden of IBD care. Endoscopic and radiologic interventions are inherently resource-intensive. Adoption of evidence-based surveillance intervals and sustainability initiatives in endoscopy may help mitigate this impact.[16] Within treat-to-target frameworks, careful alignment of monitoring intensity with clinical necessity may limit avoidable healthcare utilization and associated emissions.[5]

IBD should also be viewed within a broader environmental context. Environmental exposures, dietary patterns, and pollution have been linked to IBD risk and outcomes.[6,7,17] Diets high in ultra-processed foods have been associated with both increased IBD risk and higher greenhouse gas emissions.[18,19] Emerging microbiota-targeted strategies[20] may therefore warrant evaluation not only for clinical effectiveness but also for environmental implications across the continuum of care.

Strengths and Limitations

Strengths of this study include its prospective design, detailed patient-level activity data, and use of a standardized activity-based carbon accounting framework aligned with ISO life cycle assessment principles.[10,11] These features enabled the comparison of real-world IBD care pathways at the patient level.

Several limitations merit consideration. Emission factors were derived from published life cycle assessment sources, which may introduce estimation uncertainty. Infrastructure-related emissions and staff commuting were excluded due to allocation constraints, likely resulting in conservative overall estimates. Additionally, the single-center design may limit generalizability; however, relative differences between treatment modalities are likely applicable to similar tertiary care settings.

Implications and Future Directions

These findings support the incorporation of environmental sustainability considerations into routine IBD management through incremental, evidence-based modifications in care delivery. Future research should include multicenter validation studies. In addition, comprehensive life cycle assessments of IBD therapies should be conducted, and environmental metrics should be integrated into value-based care models. As the global burden of IBD continues to increase,[3,21] aligning effective disease control with environmental responsibility may become increasingly relevant.

CONCLUSION

Long-term management of inflammatory bowel disease is associated with a measurable carbon footprint, largely driven by treatment modality and healthcare utilization patterns. In this cohort, patient travel and biologic therapies—particularly intravenous administration—were the principal contributors to emissions.

Optimization of treatment strategies and reduction of avoidable in-person encounters, when clinically appropriate, may reduce environmental impact while maintaining standards of care. Integrating sustainability principles into IBD practice represents a practical step toward environmentally responsible healthcare delivery.

Ethics Committee Approval: The study's protocol received approval from the Ethical Committee for Clinical Investigations of the Kayseri City Hospital Non-Interventional Clinical Research Ethics Committee (Approval Number: 677, Date: 02.12.2025).

Informed Consent: Written informed consent was obtained from the patients participating in this study.

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Giant Hepatic Abscess in a Patient with Ulcerative Colitis Under Anti-TNF Therapy

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Abstract

Pyogenic liver abscess (PLA) is a significant cause of mortality if left untreated, with an incidence of 1.07 to 3.59 per 100,000 people in Western countries. PLA can result from various etiologies, including choledocholithiasis, adjacent organ inflammations such as cholecystitis, diverticulitis, and appendicitis. Additionally, immunosuppression plays a key role in the development of PLA. Anti-TNF therapies are commonly used to treat both Ulcerative Colitis (UC) and Crohn's Disease (CD). Despite the widespread use of anti-TNF therapy in inflammatory bowel disease, pyogenic liver abscesses are rare in these patients. In this report, we present a case of PLA in a patient diagnosed with UC who was undergoing anti-TNF therapy.
Keywords: Anti-TNF therapy, hepatic abscess, ulcerative colitis.

INTRODUCTION

Inflammatory bowel diseases (IBD), including Ulcerative Colitis (UC) and Crohn's Disease (CD), are chronic inflammatory conditions of the gastrointestinal tract that are typically treated with immunomodulatory and/or immunosuppressive therapies. In addition to immunomodulatory therapies, there are numerous therapeutic options available for inducing clinical remission and maintaining remission. Anti-TNF therapies are generally the first-line treatment after immunomodulatory therapies in patients with clinically and endoscopically active IBD. Anti-TNF agents are effective for both remission induction and maintenance in UC and CD.[1]

Anti-TNF therapies are associated with several well-known short- and long-term adverse events, including activation of tuberculosis, an increased risk of certain malignancies, psoriasis, and serious infections affecting the skin, respiratory system, and kidneys.[2] In addition to these, liver abscesses are rare complications.

Here, we present a case of a patient with UC undergoing infliximab treatment who developed a pyogenic liver abscess (PLA). This case was successfully managed with percutaneous drainage and parenteral antibiotic therapy.

CASE PRESENTATION

A 59-year-old male patient was admitted to our clinic with fever, chills, and abdominal pain. He had a 13-year history of Ulcerative Colitis (UC). Initially, he was treated with 5-aminosalicylate (5-ASA) agents and azathioprine for approximately one year. However, he eventually lost response to these therapies. As a result, infliximab therapy was initiated, and he had been receiving infliximab for nearly 12 years. During this time, he experienced no bleeding or diarrhea, and his colonoscopy, performed one month prior to this admission, showed remission.

Laboratory tests revealed the following results: Hemoglobin: 13 g/dL, Leukocytes: 11,900/mm³, ALT: 396 U/L, AST: 248 U/L, ALP: 193 U/L, GGT: 145 U/L, Total bilirubin: 4 mg/dL, Direct bilirubin: 3.42 mg/dL, CRP: 278 mg/dL. Initial ultrasonography showed a heterogeneous, cystic lesion measuring 12.5 x 9 cm in diameter. To further assess this lesion, a dynamic liver CT was performed, revealing a hypodense, heterogeneous, and partially cystic lesion measuring 11.5 x 10 cm with multilocular septa and a thin peripheral rim-like contrast enhancement, consistent with an abscess. This lesion was located in the inferior section of the right lobe of the liver (Figures 1 and 2).

Initially, a biliary pathology such as biliary cholangitis was suspected. However, further detailed assessment through ultrasonography and CT findings ruled out this diagnosis. A percutaneous drainage catheter was then placed under fluoroscopy into the lesion, and purulent material was obtained (Figure 3). Bacterial culture of the material revealed the presence of Streptococcus constellatus. In response, meropenem and teicoplanin antibiotic therapy were initiated.

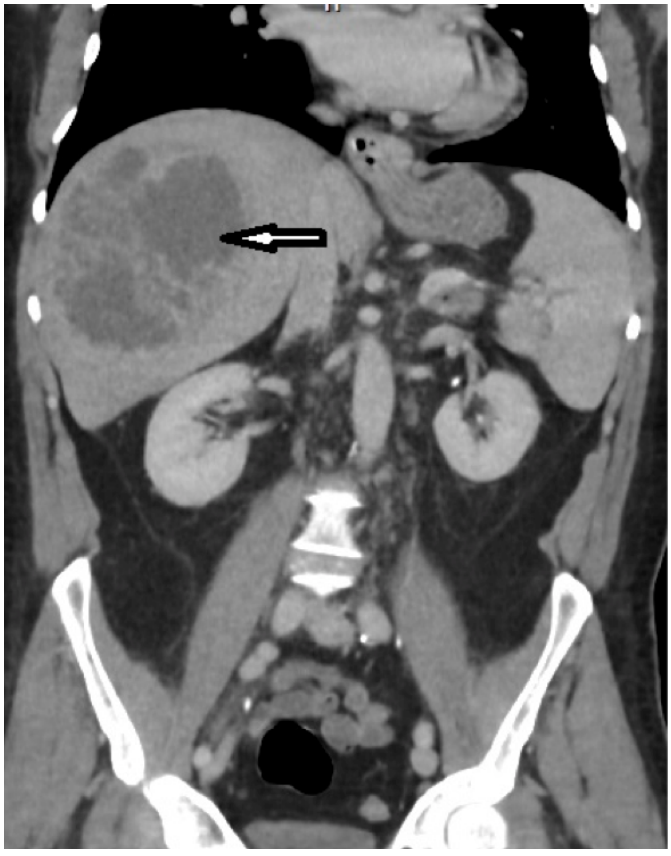

Figure 1. Hypodense, heterogeneous, and partially cystic lesion in the right lobe of the liver, observed in the coronal section.

Figure 3. Purulent material observed in the aspirate.

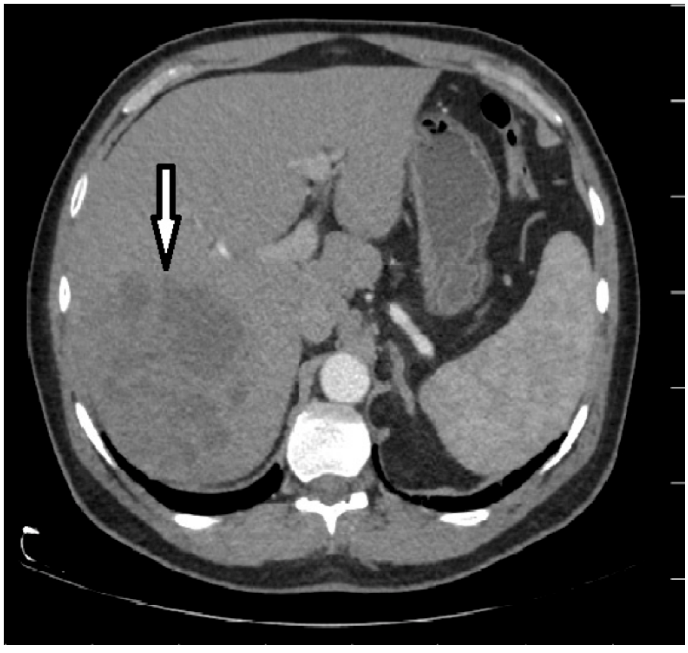

Figure 2. Abscess in the right lobe of the liver, observed in the axial section.

Under these therapies, the patient's symptoms resolved, and laboratory values improved. Two weeks after admission, CT imaging demonstrated significant improvement in the liver abscess. The percutaneous catheter was removed, and the patient was discharged after three weeks of hospitalization.

DISCUSSION

Several hepatobiliary conditions can be observed in patients with inflammatory bowel disease (IBD).[3] In some cases, the hepatobiliary system is affected as part of extraintestinal manifestations, while in others, it may be impacted due to adverse effects from medical therapies. Pyogenic liver abscess (PLA) in IBD is an extremely rare condition, according to the literature. Crohn's disease has a higher susceptibility to develop PLA compared to the general population; however, no such predisposition has been identified for Ulcerative Colitis (UC). In this case, we demonstrate that PLA can also develop in a UC patient undergoing anti-TNF therapy.

Liver abscesses are infrequently seen in IBD patients.[4] These abscesses can be either pyogenic or aseptic. Pyogenic liver abscess is a critical condition that requires prompt diagnosis and appropriate therapy. Microbial agents can reach the liver via different pathways. In some cases, adjacent inflammation, such as cholecystitis, may be the main source; in others, portal pyemia is the primary route for PLA.[5] In the general population without IBD, Klebsiella and E. coli species are the predominant pathogens. However, in IBD patients, Streptococcus species are more commonly the causative pathogens.[6] In our patient, consistent with the literature, Streptococcus constellatus was identified.

Aseptic abscess (AA) must also be considered in the differential di-

agnosis of PLA in IBD patients.[7] Histopathologically, these abscesses show abundant neutrophilic infiltration in the liver parenchyma. Aseptic abscesses can also be viewed as an extra-intestinal manifestation of IBD.[8] It is crucial to differentiate AA from PLA, and for this, the patient's clinical presentation and dynamic imaging are essential. Unlike PLA, steroids and infliximab have been successfully used to treat aseptic abscesses.[9]

Since their introduction in the treatment of inflammatory diseases such as IBD, various adverse events related to anti-TNF therapies have been described. Malignancies and infections are two of the most feared complications. Activation of tuberculosis, particularly in developing countries, is a significant concern. Other infections, including kidney infections, bacterial pneumonia, and bacterial arthritis, have also been reported in patients receiving anti-TNF therapies.[10] According to the literature, abscess formation is not a commonly described adverse event associated with anti-TNF use. However, given its immunosuppressive effect, clinicians should remain vigilant, as fever with right upper abdominal pain could signal a liver abscess in patients on anti-TNF therapies.

In summary, as with patients without IBD, early diagnosis and prompt therapy are critical for managing liver abscesses in IBD patients. Liver abscess should be considered in patients presenting with fever and right upper abdominal pain. Although uncommon in IBD patients, hepatic abscesses, as seen in our case, represent a rare but potentially severe condition.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient.

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