International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	CREATINE SUPPLEMENTATION IN INFLAMMATORY BOWEL DISEASE: LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.1(49).2026.4898
RECEIVED	10 January 2026
ACCEPTED	08 March 2026
PUBLISHED	17 March 2026
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CREATINE SUPPLEMENTATION IN INFLAMMATORY BOWEL DISEASE: LITERATURE REVIEW

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ABSTRACT

Introduction: Inflammatory bowel disease (IBD) consists of two leading types of relapsing and remitting diseases that are increasing in incidence and prevalence. The highest prevalence of ulcerative colitis (UC) and Crohn's disease (CD) has been reported in North America, the UK, and northern Europe. The incidence of IBD ranges from 5/100000/year(CD) to 9-20cases per 100000person-years, with 15–20% of patients diagnosed in childhood. Therapy usually consists of immunosuppressive medications and biologics, which carry multiple side effects. Despite it, surgery may be required to achieve remission. Creatine supplementation has been linked to improving gastrointestinal (GI) health and has potential in reducing or alleviating the symptoms of IBD.
Methodology: A narrative review was conducted using the Scopus and PubMed databases. It includes recent case reports, original studies, systematic reviews, and meta-analyses published from 1998 to 2025. All publications were analysed to explore the relationship between creatine and IBD.
Results: Creatine supplementation, primarily used in sports, is not widely used among IBD patients. Studies suggest that creatine supplementation alleviates multiple IBD symptoms. A recent case report on "creatine monotherapy" shows improvement in prior ulceration and inflammation.
Conclusions: As IBD rates increase, more research is needed to fully manage CD and UC. Creatine monohydrate supplementation shows promising results in improving gastrointestinal health. Due to the absence of randomized controlled trials and controlled clinical trials examining various dosages, further investigation is necessary to recommend it as a specific treatment.

KEYWORDS

Creatine Supplementation, Intestinal Metabolism, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis

CITATION

Aleksandra Bułat, Mateusz Sydor, Wojciech Plizga, Zuzanna Lepa. (2026) Creatine Supplementation in Inflammatory Bowel Disease: Literature Review. *International Journal of Innovative Technologies in Social Science*. 1(49). doi: 10.31435/ijitss.1(49).2026.4898

Introduction

Inflammatory bowel disease (IBD) is an umbrella term encompassing a group of chronic gastrointestinal disorders characterized by recurrent inflammation, with patterns of relapse and remission. The two principal forms of IBD are ulcerative colitis (UC) and Crohn's disease (CD), each with distinct pathological and clinical features. These conditions represent a significant global healthcare burden due to their chronicity, the need for long-term medical management, frequent hospitalizations, and impact on patient quality of life. Both UC and CD are characterized by episodic flare-ups, mucosal ulceration, dysregulated immune responses, metabolic disturbances, and impaired intestinal barrier function, which collectively contribute to complications and disease progression. Mortality risk in Crohn's disease patients is estimated to be up to 50% higher than in the general population, with approximately 25–50% of deaths attributable directly to disease-related causes such as severe malnutrition, postoperative complications, and intestinal malignancies. In ulcerative colitis, disease-specific mortality is predominantly associated with colorectal cancer (CRC) and surgical complications. Overall, IBD patients face an elevated risk of CRC, with some studies indicating an up to eightfold increase compared with the general population (Burisch et al., 2015). These data underscore the need for early diagnosis, effective therapeutic strategies, and vigilant long-term monitoring to reduce morbidity and disease-specific mortality in this population.

The etiology of inflammatory bowel disease (IBD) is the subject of extensive investigation and appears to involve a complex interplay between inherited genetic predisposition and various environmental and immunological risk factors. Approximately 50–70% of IBD patients test positive for the HLA-B27 allele (Karlinger et al., 2000), although this prevalence is lower than that observed in idiopathic ankylosing spondylitis, highlighting the need for cautious interpretation of its predictive value. Genetic studies suggest that Crohn's disease (CD) exhibits a stronger hereditary component, making it relatively more deterministic, whereas ulcerative colitis (UC) is thought to be more heavily influenced by immunological dysregulation. In addition to genetic and immune factors, psychosocial influences can significantly affect the course and severity of IBD, although they do not directly cause the disease. Stress, for example, has well-documented effects on gastrointestinal physiology, including modulation of inflammatory mediators, neurotransmitters, and gut motility (Talal et al., 1995). These findings underscore the multifactorial nature of IBD, in which genetic predisposition, immune response, environmental exposures, and psychosocial factors converge to influence disease onset, progression, and clinical outcomes.

Numerous environmental factors have been associated with the development of inflammatory bowel disease (IBD) and are considered potential contributors to disease risk. These include early-life exposures such as prenatal maternal tobacco smoking, prenatal antibiotic use, and childhood infections such as otitis media, which may influence immune system development and gut microbiota composition (Guo et al., 2023). Other recognized risk factors include aspects of lifestyle and medication use, such as urban living, which has been particularly linked to Crohn's disease (Levine et al., 2019); regular use of non-steroidal anti-inflammatory drugs and oral contraceptives, which may alter mucosal integrity or immune responses (Sokol et al., 2020); and cigarette smoking, a well-established risk factor for Crohn's disease (Faye et al., 2022). In addition, prior episodes of gastroenteritis have been implicated in increasing susceptibility to IBD, likely through transient disruption of the gut microbiome and immune dysregulation (Sudhakar et al., 2023; Yanai et al., 2022). Dietary patterns also appear to play a significant role, with consumption of ultra-processed foods associated with increased risk of Crohn's disease (Piovani et al., 2019) and western or carnivorous diets high in fat contributing to IBD susceptibility and disease severity (Lund et al., 2023; Charpentier et al., 2014). Collectively, these environmental exposures interact with genetic predispositions and immune system factors to influence the onset and progression of IBD.

As shown in Table 1, the annual incidence rates of inflammatory bowel disease vary by geographical region. As the incidence and prevalence of disease rise across all age groups, healthcare costs also increase. Using advanced therapies to treat disease progression in patients puts a substantial financial strain on the healthcare system. Patients are encouraged to seek additional treatment to help maintain remission due to the cost of therapy and the side effects of immunosuppressive medications and biologics. Another issue with current therapies is that they prioritise immune suppression and symptom control over addressing the underlying metabolic disturbances that cause mucosal injury. Recently, there has been growing interest in using metabolic modulation interventions, such as creatine supplementation (particularly creatine hydrochloride), alongside conventional treatments for inflammatory bowel disease (IBD).

Table 1. Incidence rates of inflammatory bowel disease (Caron et al., 2024).

Children and adolescents	Asia / Middle East	0.5-2.2/100 000
	Europe	1.6-10.9/100 000
	North America	11.4-13.2/100 000
Adults	Asia / Middle East	1.4-1.5/100 000
	South America	0.2-3.7/100 000
	North America	7.3-30.2/100 000
	Oceania	23.7-39.8/100 000
	Europe	10.5-46.1/100 000
Older adult	Europe	23.7/100 000

As the incidence and prevalence of disease rise across all age groups, healthcare costs also increase. The increased use of advanced therapies to treat disease progression in patients puts a substantial financial strain on the healthcare system. The cost of the treatment and the side effects of immunosuppressive medications and biologics mean that patients often seek additional treatment to help maintain remission.

Another issue with current therapies is that they prioritise immune suppression and symptom management over addressing the underlying metabolic disturbances that cause mucosal injury. Recently, however, there has been growing interest in metabolic modulation interventions, including creatine supplementation, particularly in the form of creatine hydrochloride. Research into modulators that support the healing of intestinal cells is ongoing. Not only does creatine act as a metabolic modulator, but it also has anti-inflammatory properties. These functions could serve as a potential adjunct therapy for patients with inflammatory bowel disease.

Creatine (N-aminoiminomethyl-N-methyl glycine) is part of the guanidine phosphagen family (Jäger et al., 2011). It is synthesised endogenously, primarily in the kidneys, liver, and pancreas, from arginine and glycine (Kreider et al., 2021). This provides approximately half of the body's daily creatine requirements (Brosnan et al., 2016). The remaining creatine must come from the diet (e.g., seafood, red meat, and poultry). Supplementation is a valuable source of creatine and has been shown to provide additional benefits for patients with inflammatory bowel disease who suffer from impaired intestinal absorption. Studies on creatine supplementation demonstrate beneficial effects in the treatment of inflammation-based diseases and neuroprotection, for example, in Huntington's disease (Riesberg et al., 2016).

Creatine plays an essential role in the phosphate buffering system, which maintains the correct level of adenosine triphosphate (ATP) in tissues. Creatine enters cells via a specific plasma membrane creatine transporter (CRT/ SLC6A8) (Christie, 2007). It has been shown that CRT regulates intracellular creatine levels, barrier formation, and intestinal wound healing. It has also been shown that creatine is an essential metabolic regulator of anti-tumour T cell immunity, which plays a key role in the etiology of inflammatory bowel disease. Other functions of creatine include stabilising mitochondrial permeability transition pore (mPTP), reducing oxidative damage to DNA, and lowering homocysteine and lipid peroxidation levels. It has been proven that creatine increases muscle mass and elevates muscle performance in several sports (Wallimann et al., 2011). Overall, creatine plays a pivotal role in maintaining homeostasis, especially during periods of metabolic stress and high-intensity activity.

A comprehensive understanding of the effects of creatine on intestinal health could inform the development of more effective preventive and therapeutic strategies in the future, highlighting the need for further research on this topic. This review explores the potential mechanisms through which creatine supplementation could benefit patients with ulcerative colitis (UC) and Crohn's disease (CD), drawing on current literature.

Methodology

This work was conducted as a narrative review, with a structured, reproducible literature search with the use of Scopus and PubMed online databases to identify and synthesize seminars, recent case reports, original studies, systematic reviews, and meta-analyses published from 1998 to 2025. It evaluates the role of creatine metabolism and supplementation in the context of inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC). Electronic search phrases such as "Creatine supplementation", "Inflammatory bowel disease", "Crohn's disease", "Ulcerative colitis", and "Intestinal metabolism" were used. The objective was to analyse and integrate all publications in order to explore the potential relevance of creatine hydrochloride or creatine monohydrate supplementation in relation to intestinal epithelial bioenergetics, barrier integrity, and inflammatory modulation. This analysis excluded case reports, editorials, narrative reviews, and conference abstracts without complete data, as well as non-English publications.

Results

1. Malabsorption in inflammatory bowel disease

Patients suffering from inflammatory bowel disease experience a multitude of symptoms, one of them being malnutrition due to insufficient absorption of nutrients and vitamins. The cause of malnutrition is usually anorexia, combined with reduced energy absorption and increased energy expenditure due to inflammation. The disease affecting the small intestine has a poor prognosis in terms of nutrition. Moreover, the involvement of the upper GI tract in inflammatory bowel diseases increased in recent years in both Leśniowski - Crohn disease and ulcerative colitis. While the exact frequency of upper GI involvement is unknown, Crohn's disease can affect any part of the GI tract. Short bowel syndrome (SBS) occurs when the majority of the small intestine's absorptive surface is destroyed. This occurs when the remaining surface area of the bowel is insufficient. (J. M. D. Nightingale, 2001). Common inflammatory bowel disease (IBD) symptoms such as nausea, vomiting, and diarrhoea can also hinder absorption, leading to further deterioration in nutrition.

Diffuse duodenal involvement is less common in patients with ulcerative colitis than in Leśniowski-Crohn disease. However, this does not mean that malnutrition does not occur in ulcerative colitis (UC), as it is becoming increasingly common to encounter a pancolitic presentation of the disease. Another factor contributing to reduced absorption across all IBD types is a reduction in mucosal surface area. Inflammation, ulceration, and scarring can lead to lymphatic obstruction and bacterial overgrowth, both of which cause malabsorption (Ensari et al., 2014).

The severity of the nutrient deficiency depends on the part of the digestive tract affected by the disease. SBS causes an imbalance of water and electrolytes, as well as deficiencies of both macronutrients and micronutrients. The absorption of protein, carbohydrates, and fats mainly takes place in the first 1.5 metres of the jejunum. Vitamin deficiencies (especially B12 and D) are associated with high comorbidity, leading to bone disease and impaired general well-being (Ensari et al., 2014). Impaired absorption in inflammatory bowel disease can affect the absorption of exogenous creatine, leading to impaired healing and reduced epithelial cell proliferation in the colon. These findings have prompted researchers to seek a treatment. Studies on creatine supplementation show that it is an effective way to maintain lean body mass and enhance gut metabolism in malnourished IBD patients.

2. Creatine in metabolism.

In healthy intestinal tissue, the creatine transporter is localized around tight junctions. Both ulcerative colitis and Crohn's disease are associated with decreased SLC6A8 expression. In the absence of adequate creatine, intestinal epithelial cells use a glycolysis-dominant metabolic pathway, leading to mislocalization of actin and tight junction proteins. Analysis of intestinal epithelial cells shows that CRT regulates energy balance, leading to reduced barrier function observed in patients with inflammatory bowel disease. (Hall et al., 2020) The genes that are involved in the metabolism of creatine are regulated by hypoxia-inducible transcription factors (HIFs). This regulation is critical to maintaining the barrier function of epithelial cells. In conclusion, CK activity in the intestinal mucosa is crucial. It acts as a protectant in patients with colitis due to its role in regulating HIF-1α, suggesting the potential for utilising the creatine pathway in future treatment of IBD (Wallimann et al., 2021).

Inflammatory bowel disease also alters the expression and activity of both mitochondrial and cytosolic creatine kinases (CKs), underscoring the important role of creatine metabolism in maintaining intestinal mucosal energy homeostasis and supporting epithelial repair. These alterations reflect a disruption of the phosphocreatine energy-buffering system, which is critical for rapidly regenerating ATP at sites of high metabolic demand. Such metabolic impairment may contribute to defective barrier function and delayed

inflammation resolution, thereby linking dysregulated creatine metabolism to impaired mucosal function and disease persistence (Glover et al., 2013).

Barrier maintenance requires continuous intestinal epithelial cell turnover and efficient transepithelial transport, both of which are highly energy-dependent processes. Adequate ATP availability is essential for tight junction assembly, active ion transport, cytoskeletal remodeling, and coordinated cell migration during mucosal repair. In biopsies obtained from patients with inflammatory bowel disease, significantly reduced ATP levels have been observed, reflecting impaired cellular bioenergetics within the inflamed mucosa (Schürmann et al., 1999). This energy deficit likely contributes to defective barrier function and delayed epithelial regeneration, thereby perpetuating inflammation and increasing susceptibility to luminal antigen translocation. Dietary creatine supplementation has been shown to confer protection in multiple disease models characterized by bioenergetic dysregulation, supporting mitochondrial function, stabilizing cellular ATP pools, and reducing susceptibility to metabolic stress (Klivenyi et al., 1999; Lin et al., 2011). These findings support the hypothesis that improving cellular energy buffering capacity through creatine supplementation may enhance epithelial resilience and promote restoration of barrier integrity in inflammatory bowel disease.

3. Creatine in inflammatory bowel disease.

Studies in mice have demonstrated multiple benefits of creatine supplementation in experimental models of inflammatory bowel disease. In creatine-fed mice, levels of proinflammatory mediators were significantly reduced, and intestinal infiltration by immune cells, including dendritic cells and eosinophils, was decreased, indicating attenuation of both innate and adaptive immune activation. Moreover, mice treated with creatine exhibited improved clinical outcomes, including reduced disease severity and enhanced survival rates (Glover et al., 2013). Complementary in vitro studies evaluating creatine hydrochloride further support these findings, showing that this form of creatine possesses anti-inflammatory properties and significantly reduces tumor necrosis factor alpha (TNF-α) production, a central cytokine in IBD pathogenesis (Riesberg et al., 2018). Together, these results suggest that creatine may exert both direct and indirect anti-inflammatory effects, contributing to disease amelioration.

In a 2022 study, the intestinal absorption and subsequent muscle retention of both creatine monohydrate and creatine hydrochloride were directly compared in human participants. The results demonstrated no significant differences between the two forms with respect to bioavailability, plasma creatine levels, or intramuscular creatine accumulation, indicating that both formulations are similarly effective in delivering creatine to target tissues (Kreider et al., 2022). These findings suggest that differences in chemical form are unlikely to substantially influence physiological efficacy and that standard creatine preparations may be equally suitable for therapeutic or supportive use.

It’s proven that treating mice with chronic colitis with 1 % creatine in drinking water significantly inhibits body weight loss and histological injuries. Creatine supplementation alleviated chronic ulcerative colitis by reducing macrophage infiltration into the colon (Zhu et al., 2024). Some studies have shown that creatine increases the expression of occludin and Muc2 genes, which play a role in maintaining barrier integrity (Turer et al., 2017). The barrier’s integrity is essential to long-term remissions. Creatine protects cells against metabolic and hypoxic death in vitro (Beal et al., 2011; Mooney et al., 2011). In an in vivo study, an examination concluded that creatine is necessary for maintaining epithelial cell viability under inflammatory conditions. It works by maintaining the ATP pool (Wyss et al., 2000).

Damage in both ulcerative colitis and Leśniowski–Crohn disease is primarily repaired by increased epithelial cell proliferation within colonic crypts, which enables the replacement of injured or lost cells and the restoration of the mucosal surface. When this proliferative response is impaired, epithelial regeneration is delayed, resulting in persistent barrier defects and prolonged exposure of the immune system to luminal antigens, thereby sustaining chronic inflammation. Experimental studies demonstrate that colonic tissue from mice with inflammatory bowel disease exhibits significantly reduced epithelial cell proliferation compared with healthy controls, indicating compromised regenerative capacity during active disease (Turer et al., 2017). This impaired proliferative response likely contributes to delayed mucosal healing and progression to chronic disease states.

Both epithelial cell proliferation and healing are energy-dependent, suggesting that creatine has excellent potential for both processes. Moreover, endogenous creatine synthesis occurs via glycine amidinotransferase (GATM). The loss of GATM function increases the risk of colitis and reduces mTOR-associated signaling, which is critical for epithelial regeneration (Guan et al., 2015; Sampson et al., 2016). The same study showed that creatine reversed colitis-induced injury in mice with GATM gene mutations. Also, disruptions of the mechanistic target of rapamycin (mTOR) lead to defects in intestinal epithelial cells and intestinal atrophy.

Discussion

As the global prevalence of inflammatory bowel disease continues to rise, there is an increasing imperative to invest in comprehensive research efforts aimed at improving understanding of disease etiology, progression, and long-term management strategies. Despite significant advances in biologic and small-molecule therapies, many patients continue to experience persistent symptoms, frequent relapses, treatment-related adverse effects, and impaired quality of life. Therefore, identifying safe, accessible, and cost-effective adjunctive therapies that can complement existing pharmacological approaches remains a priority. Expanding mechanistic knowledge of metabolic and nutritional factors involved in mucosal healing and immune regulation may provide new opportunities to improve patient outcomes and reduce long-term disease burden across all age groups.

Numerous studies have evaluated the safety profile of creatine supplementation in both athletic and clinical populations (Hyo Jeong Kim et al., 2011; Bizzarini et al., 2004; Juhn et al., 1998), consistently demonstrating that creatine is well tolerated at recommended dosages. These findings support the potential feasibility of creatine as an adjunctive therapeutic strategy in chronic inflammatory conditions, including inflammatory bowel disease. In addition to its established role in muscle energy metabolism, emerging evidence indicates that creatine may exert beneficial effects on intestinal epithelial integrity, immune modulation, and cellular bioenergetics, all of which are central to IBD pathophysiology. Several experimental and translational studies suggest that creatine supplementation may reduce disease activity, alleviate clinical symptoms, prolong remission periods, and improve overall patient well-being (Roy et al., 2016; Zhu et al., 2024).

Nevertheless, some reports indicate that creatine supplementation may be associated with gastrointestinal discomfort, including bloating, cramping, or diarrhoea, particularly at higher doses or with rapid loading protocols (Ostojic et al., 2008). This underscores the importance of cautious dosing strategies, gradual titration, and individualized patient assessment, especially in populations already vulnerable to gastrointestinal symptoms. However, large-scale safety evaluations and systematic reviews have found no consistent evidence of serious adverse effects associated with long-term creatine use, including in pediatric and older adult populations, leading some experts to advocate for minimal restriction on creatine supplementation when clinically appropriate (Kreider et al., 2025).

Taken together, the existing literature suggests that creatine is a promising, low-cost, and generally safe adjunct to conventional IBD therapies, with potential benefits extending beyond muscle metabolism to include epithelial protection and enhanced mucosal repair. Future randomized controlled trials in well-characterized IBD cohorts are necessary to establish optimal dosing regimens, identify patient subgroups most likely to benefit, and determine whether creatine supplementation can meaningfully affect clinically relevant endpoints, such as relapse rates, hospitalizations, and the need for surgical intervention. Until such data are available, creatine should be considered an investigational supportive therapy with a favorable safety profile and a strong mechanistic rationale for further clinical exploration.

Conclusions

Malabsorption and protein-energy malnutrition are key and clinically significant features of inflammatory bowel disease (IBD). They are caused by reduced mucosal surface area, inflammation-induced metabolic demand, dysbiosis, and, in severe cases, short bowel syndrome (SBS). These disturbances impair not only macro- and micronutrient uptake but also the availability and utilization of key metabolic substrates required for epithelial integrity and regeneration. Among these, creatine emerges as a critical regulator of intestinal bioenergetics and barrier function.

Evidence from molecular, cellular, and animal studies indicates that the creatine–creatine kinase (CK) system supports epithelial ATP homeostasis, tight junction organization, and hypoxia-adaptive responses mediated by HIF-1α. Reduced expression of the creatine transporter (SLC6A8), altered CK isoenzyme activity, and diminished ATP levels, collectively observed in IBD, contribute to barrier dysfunction and impaired mucosal healing. Restoring creatine availability shifts epithelial metabolism away from low-efficiency, glycolysis-dominant pathways and promotes cytoskeletal stability, tight junction assembly, and transepithelial transport, the processes that are essential for sustained remission.

Preclinical studies on mice consistently demonstrate that dietary creatine supplementation attenuates inflammatory signaling, reduces immune cell infiltration, preserves epithelial viability, and enhances crypt cell proliferation, thereby limiting histological damage and body weight loss in colitis models. Furthermore, the involvement of endogenous creatine synthesis pathways, particularly via GATM and mTOR-associated signaling, underscores a mechanistic link between creatine metabolism and epithelial regeneration. The

observation that creatine can reverse injury even in genetically susceptible models strengthens the rationale for targeting this pathway therapeutically.

Taken together, the current data support a model in which creatine deficiency or impaired creatine handling leads to bioenergetic failure, barrier breakdown, and delayed mucosal repair in inflammatory bowel disease (IBD), while creatine supplementation restores metabolic resilience and promotes tissue recovery. Although human clinical data remain limited, the strong mechanistic plausibility and robust preclinical efficacy of creatine as an adjunctive metabolic strategy in the management of inflammatory bowel disease (IBD) justify further investigation. Well-designed clinical trials are now needed to determine the optimal dosage, establish its safety in cases of active disease, and assess its potential alongside established anti-inflammatory and biologic therapies.

Based on this review and all available data, it can be concluded that creatine monohydrate or creatine hydrochloride is an effective additional therapy for inflammatory bowel disease, particularly Crohn's disease. Nevertheless, more extensive research is warranted. It should encompass not only larger-scale clinical trials with a long observation period, during which various doses will be considered. It seems appropriate to suggest retrospective studies involving patients with both Leśniowski-Crohn disease and ulcerative colitis, with particular emphasis on those with hard-to-achieve remissions. Depending on the results, it could become a standard adjuvant therapeutic intervention for ulcerative colitis and Crohn’s disease, to be combined with established medical treatments for these conditions. Given the evidence, supplementation may be recommended for individuals with inflammatory bowel disease.

Ethics Approval: The study was a descriptive one. No humans or animals were subjects of examinations.

Conflicts of Interest: No conflicts of interest to declare.

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