Research Article ISSN 2639-9334

Gastroenterology, Hepatology & Digestive Disorders

Glutamine as A Therapeutic Strategy in Inflammatory Bowel Diseases: A Systematic Review

Carlos Murilo Schanuel[1], Eleusa Nogueira Dias[2], Ana Paula Ferreira[3], Klaus Ruback Bertges[3] and Luiz Carlos Bertges[4*]

[1]*Medical Doctor, Gastroenterology Postgraduate, Faculdade de Ciências Médicas e da Saúde de Juiz de Fora, Suprema.*

[2]*Medical School Student, Faculdade de Ciências Médicas e da Saúde de Juiz de Fora, Suprema.*

[3]*University Professor, Faculdade de Ciências Médicas e da Saúde, Suprema.*

[4]*Coordinator, "Latu Senso" Gastroenterology Postgraduate Program, Faculdade de Ciências Médicas e da Saúde de Juiz de Fora, Suprema.*

[*]Correspondence:
Luiz Carlos Bertges, Coordinator, "Latu Senso" Gastroenterology Postgraduate Program, Faculdade de Ciências Médicas e da Saúde de Juiz de Fora, Suprema.

Received: 12 July 2019; **Accepted:** 15 August 2019

Citation: Carlos Murilo Schanuel, Eleusa Nogueira Dias, Ana Paula Ferreira, et al. Glutamine as A Therapeutic Strategy in Inflammatory Bowel Diseases: A Systematic Review. Gastroint Hepatol Dig Dis. 2019; 2(2): 1-6.

ABSTRACT

Introduction: *Glutamine is a non-essential L-α-amino acid – a polar compound due to the presence of amide groups. It is involved in maintaining the intestinal mucosal barrier, acting on gene expression, cell proliferation, differentiation, apoptosis, oxidative action, and regulation of the immune system. Due to its importance to the endothelium, glutamine has been the subject of studies for the protection and preservation of the intestinal mucosa against atrophy, which is caused by inflammatory bowel disease.*

Objective: *To verify the efficacy of glutamine in inflammatory bowel disease based on a systematic review.*

Methods: *The most relevant studies in the MedLine databases were reviewed by including randomized controlled trials only. The search strategy used the following keyword combinations: "glutamine"; "inflammatory bowel disease". To identify study designs, the following terms were used: "randomized controlled trial", "humans".*

Results: *The scope of this review included six articles with controversies regarding the efficacy of glutamine in the treatment of inflammatory bowel disease. Each study used different dosages, methods of administration and duration of administration.*

Conclusion: *According to the results, we concluded that glutamine supplementation in inflammatory bowel diseases does not cause patients any harm. Additionally, both intestinal permeability and modulation of immune and inflammatory response were improved, thus confirming the efficacy of glutamine in inflammatory bowel disease. Although these strategies are very promising and appear to be useful in some contexts, further clinical studies are needed to firmly establish the relevance of glutamine supplementation in inflammatory bowel disease. Thus, further research is needed to determine the optimal dosage, duration, route and method of administration for better use of this amino acid by the enterocytes and for maintaining homeostasis.*

Keywords

Inflammatory Bowel Disease, Treatment, Glutamine.

Introduction

The gastrointestinal tract (GIT) is a tube that has a mucous membrane covering its lumen and plays specific roles such as digesting and absorbing dietary nutrients, protecting the body against physical and chemical damage to the luminal content, and providing immunity against such damage [1,2]. The lining is made up of a single layer of epithelial cells, 80% of which

comprise enterocytes, the main role of which is the absorption of nutrients and unconjugated bile salts. They may also be involved in chemical food processing and cooperate with other cells, such as Paneth cells, in inducing immune tolerance to ingested proteins [1,2]. Paneth cells synthesize and secrete substantial amounts of antimicrobial peptides, lysozymes, which are key mediators for microbe-host interactions, including the homeostatic balance with the colonizing microbiota and innate immune protection against enteric pathogens [1,3]. The small intestine epithelium is extensively pleated to provide a very large absorption surface area, resulting in distinct villus and crypt regions in addition to the microvilli of its cells [1-4]. Below the epithelium is the lamina propria, which supports the epithelium, and both constitute the intestinal mucosa [1,3,4].

In order for everything to work properly, the enterocytes in this mucosa must have optimal conditions to play their roles. When well nourished, they prevent, among other processes, the loss of their integrity and the maintenance of their metabolic role [5]. Glutamine – a conditionally essential amino acid – becomes an essential amino acid in pathological or catabolic stress situations, as its depletion is observed to reach up to 50%, making its supplementation crucial [6]. Glutamine prevents deterioration of the intestinal permeability, protects against the development of intestinal mucosal atrophy, and improves nitrogen balance [5].

Glutamine was considered a molecule with biologically important properties in 1873 by Hlasiwetz and Habermann [7,8]. In 1935, Krebs demonstrated that cells have the ability to synthesize or degrade glutamine [8-10]. Studies with different cell types, such as lymphocytes, macrophages, enterocytes, HeLa cells, have shown that cell proliferation can be increased and cell structures and functions can be maintained in glutamine-containing culture media [11].

Glutamine is an L-α-amino acid which is synthesized from glutamic acid, valine and isoleucine, and is a polar compound due to the presence of amide groups. Two enzymes participate in its metabolism. In anabolism, the glutamine synthetase enzyme combines ammonia with glutamate to form glutamine, which is a non-toxic, neutral compound that easily crosses cell membranes. And, in catabolism, the glutaminase enzyme produces glutamate and ammonia [9]. Because it is produced by the body, glutamine is classified as a non-essential amino acid. Skeletal muscles, lungs, liver and brain have a high glutamine synthetase activity and are considered as glutamine synthesizing tissues [10]. On the other hand, some cell types, such as cells of the immune system, kidneys and intestines, have a high glutaminase activity and are therefore considered as glutamine consuming tissues [12].

Mucosal damage or interference, or imbalance in some intestinal cells, and sensitization of the normal GIT microbiota with food antigens decrease barrier functions, leading to various gastrointestinal diseases [13], among them, inflammatory bowel disease (IBD).

IBD can be divided into two main groups: Ulcerative Colitis (UC) and Crohn's Disease (CD). IBD is often associated with significant nutritional disorders such as protein-calorie malnutrition, vitamin and trace element deficiency [14].

IBD results from a multi-factor condition of an interaction between genes and environmental factors [15]. Based on genome-wide association studies, there are 163 IBD loci, 110 of which are shared between CD and UC [16].

Unlike CD, UC is confined to the large intestine with diffuse inflammation of the colonic and rectal mucosa. It is associated with the risk of colorectal cancer, which increases with the duration of symptoms [17]. In a study with Indian UC patients, the risk of colorectal cancer was 900 times higher than in the general population [17]. The UC basic mechanisms can be similar to those of CD: increased membrane permeability, immune exaggeration and decreased autophagy [18]. The Hepatocyte Nuclear Factor 4 Alpha gene (HNF4A) has been associated with UC [18]. HNF4A can regulate epithelial permeability as it controls adherent junctions, strained junctions and desmosomes, which play an important role in junctions between cells. In UC, the basement membrane can also be compromised by mutations in the CDH1 gene encoding E-cadherin and the LAMB1 laminin β1 subunit gene [18]. Another defense is through the production of anti-inflammatory cytokines such as IL-10 and TGF-β, which activate TH17 (Treg cells), which in turn suppress antigen-presenting cells and dendritic cells secreting IL-17 [18].

Faced with this pathophysiological condition, in which there is an inflammatory process of the intestinal mucosa causing injury to its cells, glutamine – the most abundant free amino acid in the human body – has been widely studied for the recovery of enterocytes. In intestinal physiology, glutamine – one of the main substrates used by intestinal cells – promotes enterocyte proliferation, regulates narrow junction proteins, suppresses pro-inflammatory signaling pathways and protects cells against apoptosis and cell stress during normal conditions [19].

Glutamine has also been shown to increase enteral blood flow, resulting in a mucosa that is more resistant to translocation by bacterial pathogens [20]. Thus, the purpose of this study was to verify through a systematic review the role of glutamine in intestinal health and its efficacy when administered as a supplementation in IBD.

Methods

The most relevant studies originally published in English, Spanish and Portuguese in the last thirty years were reviewed using the MedLine database. Only human clinical trials were chosen in search of the most clinically relevant studies.

This study used the following search keywords: "glutamine"; "inflammatory bowel disease". MeSH was referenced in order to find variations for the keywords. The inclusion and exclusion criteria are shown in Table 1.

Inclusion Criteria	Design	Clinical trials
	Patients	With Crohn's disease and ulcerative colitis.
	Intervention	Glutamine action on IBD.
	Language	English, Spanish and Portuguese.
Exclusion Criteria	Design	Case report, case series, animal models.
	Intervention	Other diseases.
	Form of publication	Abstract only
Main Clinical Outcomes	The effect of glutamine on IBD as a result of improved intestinal permeability and remission of immune and inflammatory response.	

Table 1: Inclusion and Exclusion Criteria Applied in the Selection of Studies.

Results

Eighty-one studies involving the use of glutamine in intestinal diseases and its parenteral and/or enteral use were initially identified. However, after excluding systematic review articles, articles containing only the abstract and articles related to other diseases, genetics, animals, other substances and in vitro studies, eleven studies remained. After reading the articles and excluding them by title, six articles were selected with a sample size of 111 patients. The investigation flowchart is shown in Figure 1.

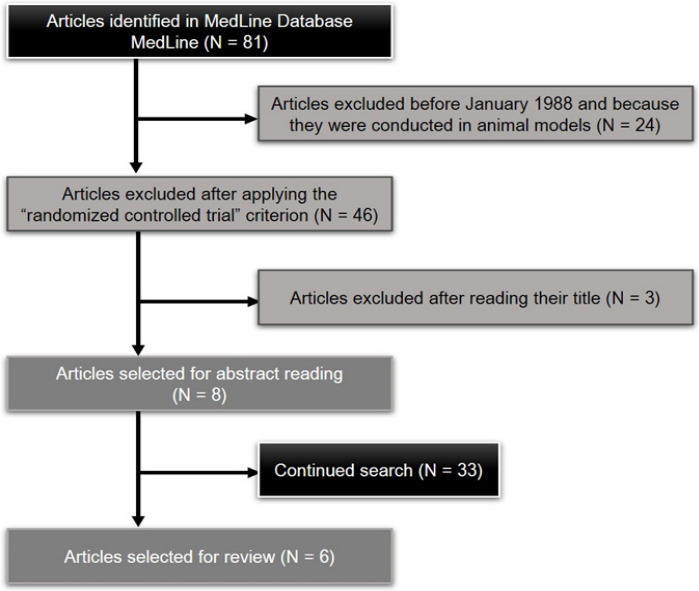

Figure 1: Study selection process flowchart.

AUTHOR	SAMPLE	METHOD/INTERVENTION	RESULTS
Akobeng et al. [5]	18 children: 9 receiving standard polymeric diet (group S) and 9 receiving Gln-supplemented diet (GG).	After 4 weeks, evaluate the PCDAI, orosomucoid level, platelet count and body weight.	There was no significant difference between the 2 groups in the proportions of patients who achieved remission: 5 (55.5%) out of 9 in group S vs. 4 (44.4%) out of 9 in GG (p = 0.500)
Coëffier et al. [34]	Duodenal biopsies conducted by UGIE on 12 healthy non-smoking volunteers (6 ♀ and 6 ♂).	A study conducted in an organ culture model with stimulation of IL-1b pro-inflammatory cytokine the production, mimicking some of its characteristics during IBD [Gln], ranging from 0.5 to 10 mM.	[Gln] increasing from 0.5 to 10 mM ↓ in vitro production of pro-inflammatory cytokines, IL-6 and IL-8, and ↑ production of cytokine AI IL-10, by the human intestinal mucosa during experimental stimulation of the inflammatory response.
Ockenga et al. [38]	24 patients with acute IBD exacerbation (19 with CD and 5 with UC) and predicted TPN >7 days.	CG received 1.5 g/kg/day AA in an acid solution (Gln-free solution), and the Gln Group received 0.3 g/kg/day alanyl-gln, which was added to 1.2 g/kg/day standard AA solution (isonitrogenic and isocaloric).	Over the 7 days of the study, Gln supplementation had no specific effect on CDAI, WBC, or CTL compared to standard TPN. There was no difference in the frequency of diarrhea, pain or EIM. Specific clinical symptoms related to UC were not evaluated due to small sample size. It also had no effect on ↓ in standard AI therapy.
Den Hond et al. [30]	14 CD patients who had increased IP.	They received 7 g Gln or placebo (glycine) 3x/day for 4 weeks.	No significant IP ↓ in patients with ↑ baseline values; no significant effect on other parameters such as CDAI, CRP, plasma Gln, plasma glutamate and ammonia, nutritional indexes.
Akobeng et al. [41]	15 active CD children, none of them having used corticosteroids or immunosuppressive agents in the past.	CG received standard diet, and the Gln Group received Gln-supplemented diet. Serum antioxidant concentrations (glutathione, vit C, vit E ...) and MDA were measured before and after 4 weeks of exclusive enteral nutritional treatment.	Mean [Se] ↑ significantly (p = 0.001). There was a significant ↓ in [vitamin C] and [vitamin E]. [Vitamin A], urate, glutathione and MDA did not change significantly throughout the study.
Benjamin et al. [31]	28 CD patients in the remission phase with abnormal IP. None with a history of using NSAID, alcohol, tobacco and protein supplements.	For 2 months, the Gln Group received 1/3 DN (0.5 g/kg/day) as a water soluble commercial preparation containing 100% Gln. CG received 1/3 DN (0.5 g/kg/day) as a water soluble WP preparation with 70% protein, 14% carbohydrate, 5% fat and minerals.	In both groups, there was a significant ↑ in both VCR and LMR, showing improvement in IP. However, the change in plasma Gln levels in both groups was not significant.

Table 2: Synthesis and Main Outcomes of IBD Glutamine Supplementation Studies.

Key: AA: Amino Acids; AI: Anti-inflammatory; NSAID: Non-Steroidal Anti-inflammatory Drug; CDAI: Crohn's Disease Activity Index; TLC: Total Lymphocyte Count; CD: Crohn's disease; IBD: Inflammatory Bowel Disease; UGIE: Upper GI Endoscopy; CG: Control Group; GG: Glutamine Group; Gln: Glutamine; [Gln]: Glutamine Concentration; PCDAI: Pediatric Crohn's Disease Activity Index; IL: Interleukin; LMR: Lactulose-Mannitol Urinary Ratio; MDA: Malonaldehyde; EIM: Ex-traintestinal Manifestations; DN: Daily Necessity; TPN: Total Parenteral Nutrition; PCR: C-Reactive Protein; IP: Intestinal Permeability; UC: Ulcerative Colitis; [Se]: Plasma Selenium Concentration; VCR: Villi-to-Crypt Ratio; WBC: White Blood Cells; WP: Whey Protein.

Discussion

The integrity of the intestinal barrier is essential for nutrient absorption and good health in humans and animals. Mechanically, the intestinal barrier is known to be maintained and regulated by gene expression and by environmental and dietary factors associated with several signaling pathways [15,21]. Any change in this barrier in the intestinal mucosa is related to increased intestinal permeability and the development of multiple gastrointestinal diseases such as IBD. Wang et al. [21] demonstrated that glutamine acts precisely in maintaining the mucosa as an intestinal barrier through the regulation of gene expression and proteins involved in cell proliferation, differentiation, apoptosis, protein turnover and antioxidant property. Additionally, glutamine also acts in the regulation of the immune system [21,22]. Given the importance of glutamine in keeping normal cell function such as those mentioned above, it is no surprise that its supplementation has been considered and examined in the clinical setting, particularly in diseases that imply impaired glutamine metabolism [19]. Thus, with several important physiological roles, glutamine is a very promising functional amino acid for the protection and maintenance of the intestinal mucosa against IBD-related atrophy.

A number of IBD animal experiments have shown that glutamine supplementation is able to protect the intestinal mucosa, increasing the possibility of glutamine use to support human patients. In one of these experiments using mice with sodium dextran sulfate-induced colitis, oral glutamine supplementation (41.7 g/kg diet; 10 days) resulted in mitigated colonic inflammatory reactions [23], as well as increased small intestine intraepithelial γδ T cell expression [24]. In another experiment [25], mice with trinitrobenzene sulfonic acid-induced colitis receiving dietary glutamine supplementation (20 or 40 g/kg; 2 weeks) showed decreased production of pro-inflammatory cytokines, including TNF-α and IL-8, bacterial translocation, and inflammation with injuries. In this latter experiment, by Ameho et al. [25], the investigators recognized that, despite the animal model findings, extrapolating the findings to the human situation is relevant for a better response to IBD treatment. Souba et al. [26] found that oral glutamine supplementation (3% in drinking water) improved abdominal radiation-induced mucosal injury and reduced bacterial translocation in the intestinal mucosa of mice. Glutamine injection (0.75 g/kg BW) in sepsis-model mice improved sepsis-induced inflammatory reactions by modulating intestinal intraepithelial lymphocytes [27,28].

Given these positive results in animal models, human studies have been conducted to support the effectiveness of glutamine supplementation in improving disease status. Sido et al. [29] found that, regarding intestinal diseases, CD patients have low plasma and cell glutamine concentrations and reduced glutaminase enzyme activity in the mucosa. These observations led to the hypothesis that glutamine supplementation would improve clinical outcomes [29]. García-de-Lorenzo et al. [22] observed that glutamine-enriched diets revealed improved immune aspects in trauma patients and improved mucositis in post-chemotherapy patients. The authors of this trial determined the amount of glutamine required for better clinical outcomes: 21 g glutamine/day for 28 days for CD, and 42 g glutamine/day for 21 days for short bowel syndrome [22].

Similarly, Den Hond et al. [30] developed a double-blind study using 21 g glutamine/day or glycine placebo at the same dose for a period of four weeks. The objective was to assess whether oral glutamine supplements could restore increased intestinal permeability in CD patients. However, there was no restoration of impaired permeability in CD [30]. A randomized clinical trial conducted by Benjamin et al. [31] showed that glutamine supplementation (0.5 g/kg BW; 2 months) in remitting CD patients reduced intestinal permeability and improved local tissue morphology. In conclusion, this study suggested that glutamine is effective for clinical improvement of CD patients [31]. Given this difference in results from these two studies, both glutamine dosage and duration of administration may influence the clinical outcome, since the route of administration was the same in both.

According to Akobeng et al. [5], a high glutamine diet (42% amino acid content) showed no significant differences between the two groups in the proportions of patients who achieved remission within four weeks. Perhaps, if they had used a lower glutamine concentration, different results would have been achieved [3]. This is due to the fact that the study conducted by Shinozaki et al. [32] suggests that excess glutamine may worsen intestinal inflammation. This study examined the effects of different enteral nutrition glutamine concentrations on trinitrobenzenesulfonic acid-induced colitis in mice. Mice were randomized into one of three treatment groups: G1, glutamine-free elemental diet; G2, an elemental diet with 12% amino acid content as glutamine; and G3, elemental diet with 24% glutamine. After five weeks, G3 mice had significantly more intestinal inflammation than G1 and G2. G2 mice had less damage than G1 mice. The investigators concluded that excess glutamine may have a deleterious effect on trinitrobenzenesulfonic acid-induced colitis, a model of Crohn's colitis [32].

Similarly, in a study by O'Dwyer et al. [33], it was shown that when 2 g glutamine per 100 mL of parenteral solution was administered to male Wistar mice, the improvement in total body nitrogen retention was greater than in animals receiving 0 or 3 g glutamine per 100 mL. It appears from these studies that there may be an optimal glutamine concentration that is beneficial in IBD and that when this concentration is exceeded, glutamine supplementation may actually be detrimental [33]. The reason for this is believed to be the formation of Nitric Oxide (NO), of which glutamine is a precursor, which may indirectly contribute to tissue damage in CD. More than 25% of metabolized glutamine in the intestine is released as citrulline. Citrulline is converted to arginine, a key substrate for NO synthesis, the production of which contributes to tissue injury and inflammation. CD, UC and glutamine are known to increase NO production by immune cells [5].

However, glutamine is known to influence cytokine production by various cell types in vitro. In a study by Coëffier et al. [34], the objective was to evaluate the effect of glutamine on pro- and anti-

inflammatory cytokine production via human duodenal biopsies cultured during experimental stimulation of the inflammatory bowel response in order to counteract the exacerbation of the inflammatory process. Increasing concentrations of 0.5 to 10 mM glutamine were found to decrease in vitro production of pro-inflammatory cytokines, IL-6 and IL-8, and increase production of anti-inflammatory cytokine IL-10 by the human intestinal mucosa. This study was conducted in an organ culture model with stimulation of pro-inflammatory cytokine production by IL-1b, mimicking some characteristics of pre- and pro-inflammatory cytokine production (IL-1b, IL-6, IL-8 or TNF-α) that are increased in IBD [34]. It is known that in IBD, including both UC and CD, dysregulation of the immune and inflammatory response is the main pathophysiological feature [35].

Novak et al. [36] conducted a meta-analysis of 14 randomized controlled trials comparing the use of glutamine supplementation in surgical and critically ill patients. Glutamine supplementation was associated with lower mortality risk (HR 0.78; 95% CI: 0.58-1.04), lower infectious complication rate (HR 0.81; 95% CI: 0.64-1.00) and shorter hospital stay (-2.6 days; 95% CI: -4.5 to -0.7). This benefit was seen mainly in patients receiving high doses (>0.2 g/kg/day) of parenteral glutamine; parenteral glutamine was associated with a significant reduction in mortality (HR 0.71; 95% CI: 0.51-0.99). These data suggest that glutamine supplementation improves the outcome of critically ill patients, mainly through a reduction in infectious complications [36]. Supported by these data, parenteral glutamine supplementation and a dosage of 0.2-0.5 g/kg/day are recommended for critically ill or injured patients [37].

Two trials were included in the review – by Akobeng et al. [5] and Ockenga et al. [38]. Although the results of these studies did not support the hypothesis that glutamine supplementation may be useful in active CD, both studies were limited by small samples, and time may have been too short for a better analysis of glutamine benefits [39]. For the primary endpoint, the punctual estimate for the hazard ratio (0.80) suggests that patients receiving a glutamine-enriched polymeric diet were 20% less likely to have a remission compared with patients receiving the standard low-dose glutamine diet. Larger trials are needed to determine if glutamine provides any benefit for inducing CD remission [39].

Although some studies have shown favorable effects, the clinical efficacy of glutamine supplementation in intestinal disease remains a conflicting issue [5], and data on IBD patients are still limited and controversial [40]. There is currently insufficient evidence to allow definitive conclusions about the efficacy and safety of glutamine in inducing CD remission. Data from two small studies – by Akobeng et al. [5] and Ockenga et al. [38] – suggest that glutamine supplementation may not be beneficial in active CD, but these results need to be interpreted with caution as they are based on a small number of patients [39]. Thus, there is a need for high-quality adequate nutrition randomized controlled trials to investigate the efficacy and safety of glutamine in inducing CD remission [39].

A decrease in glutathione concentration has been described in intestinal tissues of CD patients [41]. However, the study by Akobeng et al. [41] considered it surprising not to find a significant change in serum glutathione concentrations in the group of active CD children who received glutamine supplementation, since glutamine is a precursor in the glutathione synthesis, an important intracellular antioxidant. However, again, due to the small study sample size, no definitive conclusions should be drawn, as larger studies are needed to investigate this important issue [41].

Several factors should be considered, such as short-term glutamine administration during an outbreak phase, which could have a greater impact on outcomes than in other phases. Therefore, a need for a well-controlled clinical trial is reiterated with a population of sufficient size to determine the efficacy of glutamine supplementation in intestinal diseases [5].

Moreover, it is believed that IBD pathogenesis may also be associated with an imbalance in the intestinal microbiota, with a predominance of pathogenic bacteria and relative scarcity of protective microorganisms. Therefore, manipulating the microbiota composition would represent a great physiological and non-toxic way to prevent and treat IBD [40].

Conclusion

According to the results, we concluded that glutamine supplementation in IBD does not cause patients any harm. Nevertheless, both intestinal permeability and modulation of immune and inflammatory response were improved, thus confirming the efficacy of glutamine in IBD. Although these strategies are very promising and appear to be useful in some contexts, further clinical studies are needed to firmly establish the relevance of glutamine supplementation in IBD. Thus, further research is needed to determine the optimal dosage, duration, route and method of administration for better use of this amino acid by the enterocytes and for maintaining homeostasis.

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