



Effect of Glutamine Supplementation in Patients with Inflammatory Bowel Diseases

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Abstract

Glutamine is the most abundant free amino acid in the body and commonly classified as a nonessential or a conditionally essential amino acid in catabolic conditions. The main glutamine functions within the cell include; its role in nitrogen balance, maintaining the cellular redox state, regulation of glucose metabolism and acid base homeostasis. In addition, it has an important role in cell-mediated immunity and the integrity of the intestinal mucosa. Glutamine stores are depleted during severe metabolic stress (i.e., trauma, sepsis, major surgery, inflammatory bowel diseases, etc). Glutamine supplementation during illness increases gut barrier, lymphocyte function and preserves lean body mass. Furthermore it causes a profound improvement in intestinal barrier function in highly stressed patients. This review will discuss effects of glutamine in patients with inflammatory bowel diseases.

In vitro, animal and many recent human studies evaluated the role of several ways of glutamine supplementation including oral, enteral and parenteral rout in patients with inflammatory bowel disease. There is contradictory evidence regarding whether glutamine can improve IBD. It was reported that glutamine enriched oral diet offer no advantage in the treatment of active Crohn's disease. In addition, enteral and parenteral glutamine administration has no biochemical or clinical benefit in patients with active IBD. In contrast, limited studies concluded that orally glutamine supplementation have favorable effect on treating IBD. Briefly we can conclude that it is inappropriate to recommend glutamine for therapeutic use in active phase of inflammatory bowel diseases. Further understanding and application of glutamine-based therapeutics effects can be enhanced by future studies.

Keywords: Glutamine; Inflammatory bowel disease; Crohn's disease; Nutritional therapy

Introduction

Glutamine, or L-glutamine, is an amino acid derived from glutamic acid [1]. Glutamine is the most abundant free amino acid in the body and commonly known as a nonessential amino acid. Glutamine is present in the plasma at levels around 0.6mM and in the intracellular space at levels around 2 and 20mM. It also serves as a metabolic intermediate, contributing carbon and nitrogen for the synthesis of other amino acids, nucleic acids, fatty acids, and proteins [2,3]. Glutamine through glutamate is a glutathione precursor, a tripeptide consisting of glutamate, glycine, and cysteine, with intracellular antioxidant capacity. The main glutamine functions within the cell are separated into four categories: its role in nitrogen balance, maintaining the cellular redox state, regulation of glucose metabolism and acid base homeostasis [4]. Alkalosis with elevated ammonia level is correlated with increased production of glutamine, while during

acidosis glutamine is broken down to glutamate and ammonia serving to elevate plasma pH [2,3].

Glutamine has an important role in cell-mediated immunity and the integrity of the intestinal mucosa. Glutamine stores are depleted during severe metabolic stress (i.e., trauma, sepsis, major surgery, bone marrow transplant, inflammatory bowel disease, chemotherapy and radiotherapy. Glutamine supplementation during illness increases gut barrier and lymphocyte function and preserves lean body mass [5]. Thus, it appears that glutamine is able to down regulate proinflammatory and oxidant responses that contribute to intestinal damage [6]. Glutamine protects against septic shock by preventing the depletion of glutathione and reducing cell death, which occurs during shock. In surgical or cancer patients, glutamine supplementation decreases the production of some pro-inflammatory cytokines which may be

associated with inhibition of nuclear factor- κ B and p38 mitogen-activated protein kinase in the intestinal mucosa by glutamine supplementation to Crohn's patients [5]. Thus, it appears that glutamine is able to down regulate proinflammatory and oxidant responses that contribute to intestinal damage.

Glutamine has many benefits in the body led people to use it as a treatment for various conditions, including preventing the infections that often follow endurance exercise, reducing symptoms of over training syndrome, improving nutrition in critical illness, alleviating allergies, and treating digestive problems [1]. Glutamine, usually in the form of L-glutamine, is available by itself or as part of a protein supplement These come in powder, capsule, tablet, or liquid form [7]. Most naturally occurring food proteins contain 4% to 8% of their amino acid residues as glutamine; therefore less than 10g of dietary glutamine is likely to be consumed daily by the average person. Studies in stressed patients indicate that considerably larger amounts of glutamine (20-40g/day) may be necessary to maintain glutamine homeostasis [8]. Therapeutic dosages of glutamine used in studies ranges from 3 to 30g daily, divided into several separate doses. Glutamine is the major fuel source for cells of the small intestine, it has been proposed as a treatment for inflammatory bowel disease (IBD) [1].

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis [9]. Crohn's disease is characterized by transmural inflammation of the digestive tract and disease activity affects any part from the mouth to anus [9]. But it most commonly affects small intestine, called the ileum [10]. Ulcerative colitis is an idiopathic inflammatory bowel disease that affects the colonic mucosa and is clinically characterized by diarrhea, abdominal pain and hematochezia [11]. The exact cause of IBD is not entirely understood, it is known to involve interaction between genes, the immune system, and environmental factors [9]. Current statistics indicate 1-2 million Americans suffer from IBD, with approximately half of those cases diagnosed as Crohn's disease [12]. Ulcerative colitis is the most common type of inflammatory disease of the bowel.

It has an incidence in the UK of approximately 10per 100,000 people annually, and a prevalence of approximately 240per 100,000 [13]. The rising prevalence and incidence of inflammatory bowel disease has been recently confirmed in a global systematic review. Studies have indicated a rise in the incidence of Crohn's disease in Saudi Arabia as well as in Kuwait with almost a five-fold increase in Crohn's disease. There was a study done to collect epidemiological data on IBD outpatients and to add data from the Kingdom of Saudi Arabia (KSA) to the available IBD literature. The medical records of 693 Saudi patients with IBD over a period of 17 years, between 1993 and 2009, were reviewed. It's found that ulcerative colitis (UC) was steady throughout the years, whereas only 1.2CD patients were diagnosed per year in the first 11 years, and 73.7per year in the

last six years. IBD is no longer a rare disease in KSA. UC is in a steady state, whereas CD is increasing significantly and far outnumbering UC [14].

The extent of ulcerative colitis is variable and may involve only the rectum, the left side of the colon to the splenic flexure, or the entire colon. The typical histological (microscopic) lesion of ulcerative colitis is the crypt abscess, in which the epithelium of the crypt breaks down and the lumen fills with polymorphonuclear cells. The lamina propria is infiltrated with leukocytes. As the crypts are destroyed, normal mucosal architecture is lost and resultant scarring shortens and can narrow the colon. The severity of the disease may also be quite variable histologically, ranging from minimal to florid ulceration and dysplasia. Carcinoma may develop [11]. Although a bacterial etiology of Crohn's disease has been postulated for decades, research has never revealed a specific responsible agent. Several mechanisms for a bacterial etiology in the development of CD have been proposed: an immune response to a specific pathogen resulting in intestinal infection, alterations in normal bacterial content of the intestinal tract, a defective mucosal barrier and overwhelming exposure to resident bacteria and their antigens and endotoxins, and alterations to the intestinal immune response. Numerous bacteria including *Escherichia coli*, viruses, and parasites have been implicated in CD, but none have been confirmed [9].

The immune system usually attacks and kills foreign invaders, such as bacteria, viruses, fungi, and other microorganisms. Under normal circumstances, the harmless bacteria in the intestines are protected from such an attack. In people with inflammatory bowel disease (IBD), these bacteria are mistaken for harmful invaders and the immune system mounts a response. Cells travel out of the blood to the intestines and produce inflammation (a normal immune system response). However, the inflammation does not subside, leading to chronic inflammation, ulceration, and thickening of the intestinal wall [10]. There are many forms of Crohn's disease, the mildest form results in patches of inflammation in the lining of the intestine with of small ulcers, similar to mouth ulcers. In moderate or severe Crohn's disease, these ulcers become much larger and deeper with a lot of surrounding redness.

The inflammation can make the intestine become thickened, blocking the passage of digested food. In some cases, deep ulcers break through the wall of the intestine causing infection outside the bowel and this can then spread to the skin or a nearby part of the body. It's known as a fistula. These most frequently occur around the anus. As the inflammation heals, scar tissue may form which can in some cases also lead to a blockage in the intestine [15]. Unidentified environmental factors serve as the "trigger" that initiates the harmful immune response in the intestines. Different genetic abnormalities can lead to similar disease phenotypes; these genetic changes can be broadly characterized as causing defects in mucosal barrier function,

immune regulation or bacterial clearance. IBD can occur in people of all age groups, but the majority of cases diagnosed in adolescent and young adults ages 15-35 year. Men and women are affected equally [15].

Literature review

Effect of oral glutamine supplements in patients with Crohn's disease

There was a study done to compare the efficacy of a glutamine-enriched polymeric diet with a standard low-glutamine polymeric diet in the treatment of children with active Crohn's disease attended the Department of Paediatric Gastroenterology, Booth Hall Children's Hospital, Manchester, United Kingdom, from December 1996 through June 1998 with sample size of 18 subjects. They found that a glutamine-enriched polymeric diet offers no advantage over a standard low-glutamine polymeric diet in the treatment of active Crohn's disease [16]. In pilot study, six patients with Crohn's disease were instructed to consume 200ml of the oral nutritional supplement rich in antioxidants (AOX) and glutamine (GLN) twice daily in addition to their diet for 4 weeks. They conclude that oral nutrition supplement (ONS) rich in AOX and GLN may improve antioxidant status both in plasma and in the inflamed mucosa in patients with CD. Although the effects on oxidative stress and mucosal inflammation are not clear, these results encourage placebo-controlled studies [17].

In a randomized controlled trial, consecutive fourteen patients (age 34.5 ± 10.5 years; 20 males) with CD in remission phase with an abnormal intestinal permeability (IP) were randomized to a glutamine group (GG) or active control group (ACG) and were given oral glutamine or whey protein, respectively, as 0.5g/kg ideal body weight/day for 2 months. IP was assessed by the lactulose mannitol excretion ratio (LMR) in urine, and morphometry was performed by computerized image analysis system. They found that Intestinal permeability and morphology improved significantly in both glutamine and ACG [18]. Five studies of glutamine supplementation were performed in patients with Crohn's disease, showed no benefit of glutamine supplementation on disease activity, intestinal permeability, or nutritional indexes at doses of 21g/d, 21g/d, 15g/d, 42% compared with 4% of amino acid intake, and 12g/d, respectively. However, Zoli et al [16] study found a significant decreased in intestinal permeability. In contrast, Den Hond et al reported that no change in intestinal permeability in a much larger study. It was suggested that both glutamine-stimulated T cell function and the metabolism of glutamine to nitric oxide might actually increase intestinal inflammation [19].

A Systematic Review in 2003, Ninety-one studies were assessed the benefits of enteral administration of glutamine in Patients older than 18y with different pathologic conditions includes postsurgical patients, septic patients, critically ill patients, and patients with multiple trauma and inflammatory

bowel disease, short bowel syndrome, and bone marrow transplantation and burn patients. Only 16 studies confirmed the good clinical tolerance of enteral and parenteral glutamine. One well designed study in patient with Cohn's disease that did not report that glutamine, given in oral doses of 21g/d for 28d in addition to a standard diet, improves intestinal permeability as assessed by 51 Crethylene-diamine-tetraacetic acids. The study included a small number of patients, and this may have been the reason significant results were not detected [20].

Effect of oral glutamine supplements in patients with ulcerative colitis

Other study investigated the effects of dietary glutamine (Gln) on T-helper (Th) and T regulatory (Treg) cell homeostasis and colonic inflammatory mediator expression in mice with dextran sulfate sodium (DSS)-induced colitis. The findings of this study showed that dietary Gln supplementation before and during colitis modulate the homeostasis of Th and Treg cells that may mitigate colonic inflammatory reactions. Besides, the partial elemental component provided by Gln diet may also have favorable effect on treating IBD [21]. Recent studies indicate enhanced heat shock protein (HSP) expression is a key mechanism underlying glutamine (GLN) protection. Experimental colitis was induced in rats via oral 5% dextran sulfate sodium (DSS) for 7 days. GLN (0.75g/kg/d) was administered to rats by oral gavage during 7-day DSS treatment. These data demonstrated the therapeutic potential of GLN as a "pharmacologically acting nutrient" in the setting of experimental IBD, the enhanced HSP expression observed following GLN treatment may be responsible for this protective effect [22].

Other study examined serum amino acids profile in dextran sulfate sodium (DSS)-induced colitis, and impacts of graded dose of arginine or glutamine supplementation on the colitis. Using DSS-induced colitis model, which is similar to human ulcerative colitis, they determined serum profile of amino acids at day 3, 7, 10 and 12 (5 days post DSS treatment). It concluded that Dietary arginine or glutamine supplementation had significant ($P < 0.05$) influence on the clinical and biochemical parameters (T-SOD, IL-17 and TNF- α) in colitis model, so, arginine or glutamine could be a potential therapy for intestinal inflammatory diseases [23]. Shinozaki et al observed significantly increased colonic inflammation in a rodent model of ulcerative colitis in which rats were fed a diet supplemented with 24% glutamine, although those animals that received a lesser amount of glutamine had the least inflammation. They found that the disease activity index actually improved more in the control group than the glutamine-supplemented group [16].

Enteral and parenteral administration of glutamine in patients with inflammatory bowel disease

Other study done to determine whether chronic intestinal inflammation alters glutamine utilization in six patients with Crohn's disease and 6 healthy subjects received 7-h

intravenous infusions of L-leucine, along with L-glutamine delivered intravenously for the first 3.5h, and via a nasogastric tube for the subsequent 3.5 hrs. This study demonstrated that at remission state, patients with Crohn's disease have normal rates of proteolysis, and glutamine production, utilization, oxidation, and splanchnic uptake. The data suggest there is no obvious requirement for glutamine in patients with quiescent Crohn's disease [24]. Glutamine supplementation causes a profound improvement in intestinal barrier function in highly stressed patients and patients in total parental nutrition (TPN). Glutamine-fortified parenteral and enteral diets significantly improve the intestinal morphology and function [25]. Other experimental data support the importance of glutamine in GI function. Rats fed via parenteral nutrition showed less mucosal atrophy when supplemented with glutamine [26].

A randomized study included 24 patients with an acute exacerbation of IBD (19 Crohn's disease; five ulcerative colitis) and scheduled for total parenteral nutrition (TPN) (>7 days), reported that Glutamine-enriched total parenteral nutrition has no biochemical or clinical benefit in patients with active IBD [27]. Several RCTs have been conducted to evaluate the efficacy of glutamine supplementation in enteral or parenteral nutrition treatment in humans (64-66); however, none have been able to demonstrate any additional benefits for the glutamine-supplemented groups [27]. A recent study of 52 patients hospitalized with acute pancreatitis or inflammatory bowel disease compared the use of glutamine-supplemented TPN and standard TPN in a group. A shorter length of stay was found in the patients with pancreatitis who received the glutamine-supplemented TPN but not in the patients with inflammatory bowel disease [28]. There was a study assessed the effect of glutamine pre-treatment in vivo and in vitro on cytokine production by intestinal mucosa in nine fasted volunteers received either enteral glutamine or saline over 6 h in a cross-over design. They concluded that glutamine reduces pro-inflammatory cytokine production by human intestinal mucosa; it could be useful to modulate inflammatory conditions with imbalanced cytokine production [29].

Discussion

Inflammatory bowel disease (IBD) involves chronic inflammation of all or part of digestive tract. IBD primarily includes ulcerative colitis and Crohn's disease [9]. The incidence and prevalence of IBD are increasing with time and in different area around the world, indicating its emergence as a global disease. Many studies suggest that there are a relationship between glutamine supplementation and IBD. We have reviewed in vitro, animal, and human studies concerning several ways of glutamine supplements in patients with Crohn's disease. Only one study reported that oral glutamine have a positive effects of Intestinal permeability and morphology [18]. The study included a small number of patients with CD in remission phase and this may have been the reason significant results not detected. In contrast, eight studies showed no advantage of supplemented

oral glutamine in the treatment of active Crohn's disease (no benefit on disease activity and intestinal permeability).

Enteral feeding of glutamine reduced pro-inflammatory cytokine production by human intestinal mucosa; it could be useful to modulate inflammatory conditions with imbalanced cytokine production. In animal study, rats fed via parenteral nutrition showed less mucosal atrophy when supplemented with glutamine [26]. Although it is controversial to whether glutamine supplementation reduces intestinal inflammation [24], Radha K et al observed Glutamine-fortified parenteral and enteral diets significantly improve the intestinal morphology and function. In contrast, four studies in patients with IBD found that parenteral glutamine administration has no biochemical or clinical benefit in patients with active IBD. ESPEN's published clinical guidelines, use of PN glutamine supplementation could not be recommended in patients with inflammatory bowel disease, intestinal failure, due to insufficient evidence for benefit [30].

Two studies of supplemented glutamine in patients with ulcerative colitis, showed that dietary Gln supplementation modulate the homeostasis of Th and Treg cells that may mitigate colonic inflammatory reactions. Partial elemental component provided by Gln diet may also have favorable effect on treating IBD [21]. Hongyu X et al, demonstrated that GLN as a "pharmacologically acting nutrient" in the setting of experimental IBD by enhancing heat shock protein expression. Although many of the experimental models of inflammatory bowel disease have demonstrated beneficial effects of glutamine supplementation, one recent study suggest that excess glutamine may worsen intestinal inflammation Shinozaki et al. Further large scale trials are needed to determine the efficacy of glutamine in IBD.

Conclusion

On the basis of currently available clinical data, it is inappropriate to recommend glutamine for therapeutic use in active phase of inflammatory bowel diseases (excess glutamine may promote inflammatory activity). Further understanding and application of glutamine-based therapeutics effects can be enhanced by future studies.

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