

## The Effects of Glutamine in the Treatment of Irritable Bowel Syndrome

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### Abstract

This systematic review study aimed to analyze the effects of glutamine on irritable bowel syndrome, demonstrating the adequate dose of glutamine for the treatment of IBS and identifying which clinical symptoms are improved with glutamine supplementation that include a relationship with the restoration of the intestinal wall, increase of immune cells, among other effects. Forth research, a systematic literature review of articles published between 2011 and 2021 was carried out. The research demonstrated that glutamine supplementation helps to protect the intestinal mucosa, increasing the capacity of immune cells, decreasing the translocation of bacteria and toxins after intestinal injury, preventing infections and inflammation, improving the symptoms of individuals with IBS. It is concluded that glutamine supplementation enhances the synthesis of this amino acid, which is extremely important in situations of metabolic stress and to exercise activities related to intestinal villi, consequently improving nutrient absorption.

**Keywords:** Irritable Bowel Syndrome; Treatment; Glutamine; Immune cells

### Introduction

Glutamine is a molecule with biologically important properties, being nutritionally classified as a non-essential amino acid, since the body can synthesize it. L-Glutamine is classified as a five-carbon amino acid that, at physiological pH, is an important cellular substrate not only because it is an amino acid, but also because it is a source of nitrogen and carbon energy for the synthesis of other molecules; an important energy source for macrophages, lymphocytes and other cells of the immune system [1].

According to Santos [2], it is in the skeletal muscle that the regulation of glutamine occurs, especially in situations of great metabolic stress, in which the tissues need greater amounts of energy. In these situations, the demand for glutamine for other organs is increased, since it works as a cellular signaling agent, helping to modulate genes related to protein synthesis and degradation, by participating in gluconeogenesis, acting in the maintenance of the immune system.

In situations of intense and prolonged physical exercise, in great stress, such as burns and diseases caused by HIV, the amount of phagocytic cells of the immune system is reduced, allowing the development of opportunistic infections. Glutamine, in these cases, is used as energy by the cells of the immune system for the formation of antibodies, as well as fuel for the cells of the immune system, acting in the synthesis of nucleotides and providing an efficient duplication of phagocytic cells [3].

Studies have shown that patients with high metabolic stress, when supplemented with glutamine, developed increased RNA synthesis, improving immune function. The explanation for this was that, by presenting a reduction in the glutamine synthetase molecule, these patients showed a decrease in the action of the immune system, since these cells start to depend only on plasma glutamine for RNA synthesis, compromising the immune response and triggering high risk to infections, since glutamine in insufficient amounts for the body favors the decrease of immunity [4].

A factor that has been made possible by science is the use of glutamine in Irritable Bowel Syndrome (IBS) because as it deals with gastrointestinal imbalances, it also encompasses intestinal irritation, which can be controlled with supplements that help these cellular dysfunctions, as being studied glutamine [4].

IBS is a condition that mainly affects women and individuals between 15 and 65 years of age, triggering symptoms such as psychological changes, depression or stress, favoring the worsening of the clinical picture. Normally, in the first manifestations, individuals do not seek medical help, only after symptoms persist in the 30 to 50 age phase [5].

The treatment of IBS is usually also based on the symptoms and the association with psychosocial disorders, such as: changes in lifestyle, changes in diet, drug treatment, in some cases, psychological treatment and use of probiotics [5].

The individual's relationship with stress is one of the psychosocial factors that play a greater etiological role in IBS, although it is not determinant, and may interfere with intestinal functioning through changes in motility or spasm, in the decrease or increase of secretion and, consequently, in the irritation of the intestine. Psychosomatic diseases are caused by emotional problems of the individual, also called somatization disorders, including physiological mechanisms, intestinal motor dysfunctions and neuroendocrine changes, so that, according to some experts, after these findings, psychotherapy may be indicated as an intervention to control stress. in individual cases [6].

The diagnosis of Irritable Bowel Syndrome (IBS) is still difficult to make, despite being a highly prevalent condition, with very individual clinical pictures, interfering in a very negative way in the quality of life of its patients and being the most representative disease of the world. brain-gut axis [7].

The motor activities, between the Central Nervous System (CNS) and the intestine, occur from sensory and autonomic reactions of the digestive tract, continuously modulated by higher neural centers of the CNS. External or cognitive information recognized by the neural connections of the digestive tract with the CNS are also capable of controlling, altering secretion and digestive sensations, thus altering the function of the gastrointestinal tract [8]. According to Silva [9], multidisciplinary follow-up as well as psychological, social, nutritional and educational support should be considered important determinants to maintain or improve the quality of life of these patients.

With aging, the individual begins to undergo changes in their Gastrointestinal Tract (GIT), with a significant loss of their microbiota, which can cause damage to their health, so that the symptoms of individuals over 50 years of age begin to encompass changes in habit, bowel, involuntary weight loss and pain when defecating, considered as an alarm signal to be investigated [10].

The objectives of this systematic review are to analyze the effects of glutamine on IBS, informing the appropriate dose of glutamine for the treatment of IBS and analyzing which clinical symptoms of IBS are improved with glutamine supplementation.

### Material and Methods

This research was a systematic review of the literature, where the search for articles was performed in PubMed, Lilacs and Scielo databases. Scientific articles were used with data on evidence, clinically relevant, according to the information that was obtained from research investigations. Articles in English, Spanish and Portuguese were selected that addressed Irritable Bowel Syndrome, the treatment for Inflammatory Bowel Diseases, glutamine and the use of glutamine in the treatment of Irritable Bowel Syndrome

and Inflammatory Bowel Diseases. Inclusion criteria were articles published between 2011 and 2021, which evaluated humans and animals; articles with dates different from the established period were excluded, in addition to the exclusion of articles that deviated from the topic addressed.

## Results and Discussion

From the literature search, 10 studies were gathered that fit the parameters sought. Table 1 presents some data from these articles, with description of authors/year of publication; number of people who participated in the sample (N); genre; age; time of use and dose of glutamine used; and whether there was a relationship between glutamine and improved bowel function.

<i>Author/Year</i>	<i>Study location</i>	<i>Time of use and dose of glutamine</i>	<i>Sample group(N)</i>	<i>Result</i>
Zuhl et al., 2014 [10]	Mexico; study Randomized	7 days;200mg	15 individuals: 8 men 5 women, aged 18 to 45 years	Beneficial for Intestine
Caporossi, 2019 [11]	Mato Grosso, Brazil; study Randomized	7 days;300mg	120 individuals aged 18 to 50 years	Beneficial for Intestine
Nagmaniyatala., 2012 [12]	United States; double randomized controlled trial	30 days;500mg	20 subjects with low plasma alanine level; oral supplementation	Beneficial for Intestine
Arnal, 2016 [13]	Amsterdam; controlled study	30 days;50mg	10 subjects with administration intravenous route	Beneficial for Intestine
Vasconcelos, 2002 [14]	China; controlled study	46 days;300mg	18 severely ill individuals with infectious complications	Beneficial for Intestine
Verne, 2017 [15]	United States; study double-blind randomized	8 weeks;5g	52 individuals; oral supplementation	Beneficial for Intestine
Ferreira, 2020 [16]	Ceará, Brazil; randomized study	20 days;5g	14 septic individuals	No change to Intestine
Vermeulen et al., 2016 [17]	Netherlands	30 days;5g	20 septic individuals in a non-critical state	Beneficial for Intestine
Hippolyta, 2016 [18]	São Paulo, Brazil; study randomized	14 days;150mg	30 adult Wistar male rats	No change to Intestine
Bruyne et al., 2016 [19]	USA	15 days;200mg	10 animals with gastrointestinal symptoms	Beneficial for Intestine

**Table 1:** Methodological aspects used for the results of the studies.

According to studies by Zuhl et al. [10], in which groups of men and women with common characteristics were analyzed, who used drugs (anti-inflammatory, antidepressants or diuretics), it was observed that the administration of 200mg of glutamine during 7 days in 115 subjects significantly improved intestinal stability, as well as decreased gastrointestinal stress in 62% of cases. Similar results were also reported in studies by Vasconcelos [14], carried out with 18 sick adults, where the administration of glutamine lasted 46 days, with 300mg per month, with a reduction in infection in the studied sample.

Likewise, Nagamani et al. [12] also observed in their studies carried out with a group of 20 patients that supplementation of 500mg of glutamine for 300 days was efficient, reducing the rate of infectious complications in adults with critical illness or undergoing elective surgery, as well as a significant improvement in intestinal dysbiosis in 70% to 87% of supplemented individuals, when compared to the other non-supplemented group. In addition, the authors observed that supplemented individuals had a shorter hospital stay, ranging from 2 to 9 days, with improved quality of life with continued use of glutamine.

In the study by Verne [15], carried out with 52 individuals who received 5mg of oral supplementation for 8 weeks, once a day, it is highlighted that the use of glutamine in 68% of the analyzed cases demonstrated a decrease in intestinal oxidative stress, that is, it was effective in irritable bowel syndrome, dramatically and safely decreasing all major Syndrome-related outcomes such as flatulence, cramps, constipation and mucus in the stool.

According to Arnal [13], who analyzed 10 individuals with 50mg of glutamine administered intravenously for 30 days in patients with gastrointestinal malabsorption, plasma renewal was observed in 58% of the cases supplemented with glutamine. Likewise, Caporossi [11] also observed benefits with supplementation in his study, carried out with 120 individuals followed up with outpatient clinical analyses. Immunocompromised patients started glutamine supplementation with 300mg for 7 days, noting that this supplementation improved the presence of immune defense. However, it was observed that an increase in the dose offered may be necessary to achieve a significant impact.

According to Vermeulen et al. [17], through a study with 20 septic patients who received 5mg of glutamine for 30 days, plasma concentrations of citrulline increased significantly with supplementation, triggering an improvement of 68%.

In the study carried out by Bruyne et al. [19] with animals, including 10 adult mice supplemented with 200mg for 15 days, energy supply was observed from rapidly dividing cells, such as intestinal epithelial cells and immune system cells in 98% of the animals. used in comparison to another study carried out with 30 adults male Wistar rats with glutamine administration of 150mg for 15 days, which showed low alteration to the intestine according to Hypólito [18].

Considering that irritable bowel syndrome (IBS) is a risk factor for many more serious diseases, such as cancer of the digestive tract, and is a chronic disease, with late diagnosis, that affects men and women of all age groups worldwide, with worldwide prevalence from 10% to 20% [9], more studies are needed to confirm these results, and to determine the best dosing regimen and timing for this indication, and longer-term studies are needed to determine whether glutamine has a significant effect on other conditions or pathologies.

According to studies by Zuhl et al. [10] in individuals with intestinal permeability and systemic inflammation associated with gastrointestinal discomfort showed that there was a significant improvement in intestinal stability and a decrease in gastrointestinal stress in 62% of cases, demonstrating the protective action of glutamine through preservation of the intestinal barrier and modulation of the inflammatory response.

The protective effect of glutamine in the intestine occurs through the activation of the HSF-1 protein, leading to the expression of the heat shock protein HSP70, through HBP (hexosamine biosynthesis). This occurs because HBP divides in the glycolytic pathway by walking through fructose-6-phosphate, allowing glutamine to act as a key substrate, leading to the activation of N-acetylglucosamine, which plays an important role in regulating the transcriptional response to stress.

Caporossi [11] points out in his study that supplementation with glutamine positively modified the metabolic condition of patients in 7 days, noting that, with the supplementation of this amino acid, the immune defense of the host increases. The author also pointed out that a time greater than 7 days with supplementation and increasing the dose offered may have a superior positive result.

Another point of the research is that glutamine is used in gluconeogenesis, in lymphocyte production and proliferation (energy substrate for lymphocytes) and also in stimulating the immune response in healing and mucosal functions, where the promotion of gut integrity is one of the benefits. most cited in glutamine supplementation. It was observed that the amino acid acted on oxidative stress,

fatigue and intestinal cellular absorption. Research results indicate that glutamine may have a potential mechanism in stimulating pancreatic glucagon secretion, thus decreasing the proportion of insulin [11].

The effect of glutamine in the treatment of IBS was also observed in a study carried out by Nagamani et al. [12], with 20 patients, which showed an 80% reduction in the severity of IBS symptoms and also an improvement in the frequency of peristalsis and intestinal permeability during IBS-related diarrheal attacks. Divided into two groups, part of these patients received 5g of glutamine powder orally and the other group received placebo, for a period of 8 weeks in 3 times a day, showing positive results in the treatment of intestinal inflammation, reducing the infiltration of macrophages in the cavity. Peritoneal and also the production of pro-inflammatory cytokines in the colon.

According to studies by Arnal [13], with the intravenous administration of 50mg of glutamine for 30 days, it showed a reduction in the symptoms of phenotypic conditions and diseases associated with intestinal dysbiosis, obtaining the same result found in the controlled trial carried out by Ferreira [16], which found visceral hypersensitivity of the intestine.

Verne [15] explains that in patients with great stress and metabolic demand, there is an intestinal imbalance, which makes them need supplementation, since glutamine increases the system in which macrophages and lymphocytes act, stimulating the increase of defense cells and helping in repairing the intestinal mucosa.

According to a study by Hypólito [18], it is observed that previous supplementation in experimental animals (rats) with intraperitoneal glutamine reduced the damage caused to the intestinal mucosa, kidney and liver histoarchitecture, since glutamine is essential for the proliferation of epithelial cells of the intestine, which may be essential for intestinal homeostasis during catabolic states, when glutamine levels are replenished, and in stressful situations, the affected mucosa can be regenerated.

Another study, by Bruyne et al. [19], carried out in 2016 with animals, indicated an increase in the supply of rapidly dividing cells and cells of the immune system with the supplementation, demonstrating that, when a muscle injury occurs, the defense cells are signaled for tissue recovery, including lymphocytes and macrophages, which use glutamine as a fuel source. When there is some inflammation of muscle tissues (a transcription factor that acts to control the expression of genes linked to inflammatory responses), glutamine has a positive response [12].

Taking into account the results found in the aforementioned studies, it was observed that the supplementation of approximately 5g of the amino acid glutamine 3 times a day in the treatment of IBS is beneficial, since glutamine acts by increasing the activity of the immune defense cells. intestine, acting in the prevention of infections and inflammations, although the studies that relate the treatment of IBS with glutamine supplementation are still few [11-14].

### Conclusion

According to the data obtained in the subject in question, which evaluates the effects of glutamine on Irritable Bowel Syndrome, it was possible to observe that this amino acid has a beneficial effect on the restoration of the intestinal mucosa in most cases addressed.

Studies indicate that glutamine is essential for the production of energy in the cells of the immune system and in the prevention of infections and inflammation, increasing intestinal permeability in situations of great metabolic stress, significantly improving symptoms, because when the individual has IBS the immune system is weakened, which ends up favoring problems that it generates such as: abdominal pain, gas, periods of constipation and diarrhea.

However, additional studies are still needed for a better understanding of glutamine action, specifically in IBS, which has different intensities in its manifestations.

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