Glutamine supplementation in gut flora recovery

Suplementação de glutamina na recuperação da flora intestinal

La suplementación con glutamina en la recuperación de la flora intestinal

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RESUMO

Objetivo: evidenciar através de uma revisão integrativa os resultados clínicos atuais da suplementação de glutamina na melhora da saúde intestinal, através de sintomas e exames bioquímicos. **Método:** Revisão integrativa da literatura realizada no período de setembro de de 2021 nas bases de dados Pubmed e Scielo. **Resultados:** Foi realizado uma busca pelos descritores em saúde determinados e foram selecionadas 08 produções cientificas que atenderam os critérios de inclusão. **Conclusão:** Sugere-se novas pesquisas que elucidem as dosagens, efeitos colaterais e respostas terapêuticas da glutamina sobre parâmetros de saúde intestinal.
Descritores: Intestino; Alimentação; Nutrição.

ABSTRACT

Objective: to evidence through an integrative review the current clinical results of glutamine supplementation in the improvement of intestinal health, through symptoms and biochemical tests. **Method:** Integrative review of the literature conducted in the period of September 2021 in the Pubmed and Scielo databases. **Results:** A search was performed for the defined health descriptors and 08 scientific productions were selected that met the inclusion criteria. **Conclusion:** Further research is suggested to elucidate the dosages, side effects and therapeutic responses of glutamine on intestinal health parameters.
Descriptors: Intestine; Food; Nutrition.

RESUMEN

Objetivo: evidenciar a través de una revisión integradora los resultados clínicos actuales de la suplementación con glutamina en la mejora de la salud intestinal, a través de síntomas y pruebas bioquímicas. Método: Revisión integradora de la literatura realizada en el periodo de septiembre de 2021 en las bases de datos Pubmed y Scielo. Resultados: Se realizó una búsqueda de los descriptores de salud definidos y se seleccionaron 08 producciones científicas que cumplieron con los criterios de inclusión. Conclusión: Se sugiere investigación adicional para dilucidar las dosis, los efectos secundarios y las respuestas terapéuticas de la glutamina en los parámetros de salud intestinal.
Descriptores: Enfermería; Infección de la herida quirúrgica; Unidad de Cuidados Intensivos.

Introduction

Gastrointestinal disorders are characterized by changes in tissues and organs of the gastrointestinal tract. Manifestations are signs and symptoms such as nausea, abdominal pain and burning, originated from a underlying disease. Approximately 27% of the world's population has constipation, one of several disorders that can affect the gastrointestinal tract.[1]

Nutritional therapy is used to aid intestinal health. The adjustment in the diet occurs mainly in order to prevent or correct malnutrition, supplement nutrient deficiencies and reverse part of the pathological metabolic consequences. Nutritional therapy acts as an adjunct together to clinical or surgical treatment, however, in specific cases it may become the main treatment.[2] The search for effective supplements to improve intestinal health is one of the major paradigms of medical research today.

Glutamine is a non-essential amino acid found in significant amounts in the human body. It is the largest amount of free amino acid present in plasma and muscle tissue, comprising about 20% of the free amino acids in the blood. Glutamine synthesis occurs in muscle tissue and has as precursors asparagine and glutamic acid.[3]

The functions of glutamine are broad and essential to the organism, being responsible for nitrogen transport; Gluconeogenesis; acid-base regulation; cell proliferation; and glutathione biosynthesis. And in the presence of severe catabolic stress, its intracellular concentrations may run out. This amino acid is an essential fuel for rapidly proliferating cells, including intestinal epithelial cells and lymphocytes. In addition, it is the primary fuel for the gastrointestinal epithelium and maintains the structure of the mucosa.[4,5]

Glutamine regulates intestinal barrier function in lesions, infections, weaning stress and other catabolic conditions. These effects are mediated by maintaining intracellular redox status and regulating gene expression associated with various signaling pathways.[6]

In vitro and animal studies have already shown the relationship between glutamine deficiency and intestinal homeotase failure that occurs during physiological stress.[7]

The scheme proposed by Kim and Kim (2017) demonstrates that glutamine maintains intestinal tissue integrity by promoting enterocyte proliferation, activation of thyrogen-activated protein kinases (MAPKs, (ERK1/2, JNK1/2), optimizing the actions of growth factors (epidermal growth factor (EGF), insulin-like growth factor (IGF)-I, transforming growth factor (TGF)-α) and inducing the expression of narrow-junction proteins (claudione-1, claudiine-4, ocludine, occludent zonula (ZO)-1, ZO-2 and ZO-3).[8]

Pro-inflammatory signaling pathways, such as nuclear-κB factor (NF-κB) and signal transducers and transcription activators (STAT), are inhibited by glutamine and amino acid also suppresses extensive apoptosis by participating in glutathione synthesis (GSH) and regulating the expression mediated by thermal shock factor (HSF)-1 of thermal shock proteins (HSPs). Therefore, glutamine improves endoplasmic reticulum (RE) stress and promotes autophagy by inhibiting the mechanistic target of the rapamycin pathway (mTOR), thus

protecting intestinal cells from stressful conditions. T bars mean inhibition while arrows represent stimulation.[8]

The results of glutamine supplementation in clinical trials are still controversial. Despite the potential dose-dependent benefits, gastrointestinal tract tolerance to high-dose acute oral glutamine supplementation is not positive.[9]

Based on the evidence presented so far, the aim of the present study was to evidence through an integrative review the current clinical results of glutamine supplementation in improving intestinal health, through symptoms and biochemical tests.

Method

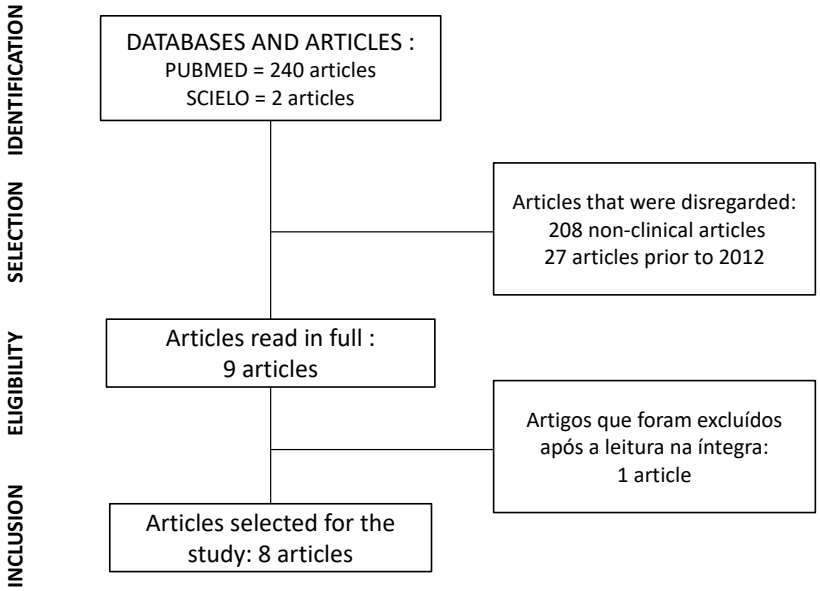
The work is an integrative review of the literature. Data were collected in September 2022. The literature review was limited by studies addressing variables related to the use of glutamine in order to verify the improvement of gastrointestinal symptoms or results of biochemical tests that were related to the above.

The study also sought articles that included only studies with human beings (of both sexes and regardless of age group) and did not exclude pathologies of the gastrointestinal tract.

The descriptors used for this research were: gut/gut and/and glutamine supplementation supplementation. The databases were: Pubmed and Scielo, in the last ten years (2012-2022) in English and Portuguese.

The first search resulted in 242 articles, and after screening per year, title and clinical studies, we selected 9 papers that were read in full to be eligible according to their methodologies and objectives. The reading of the manuscript titles and their final selection were performed by the pairs.

Figure 1- Publication selection flowchart for integrative review, 2022.



After reading the full studies, it was found that 1 article did not meet the inclusion criteria. The articles included in the research were 8 international studies, which included the use of glutamine supplementation and evaluated intestinal health parameters, encompassing clinical symptoms and biochemical analyses.

Results and Discussion

Nine articles were identified in this integrative review, interpreted and reduced by comparing the data exposed in the investigation of the theoretical framework, according to Chart 1.

Since, among the articles included in this literature review, different experimental designs were observed, it was decided to emphasize the following data: supplement used (within glutamine variations), route of administration, target audience, intervention time, results and side effects.

Chart 1- Distributions of the articles found according to reference, objective, supplement, route of administration, target audience, intervention time, results and side effects.

Author	Objective	Suplement	Route	Target audience	Time of Intervention	Results
Mitter et al., 2012	To evaluate whether apolipoprotein E4 affects intestinal barrier function, thus improving short-term growth and long-term cognitive outcomes in children from Brazilian slums.	Vitamin A (100,000 IU of retinil palmitate or 200,000 IU of retinil palmitate every four months), zinc (40 mg twice a week) or both for 1 year, with half of each group receiving glutamine (16 g per day).	Oral	Children	1 year	Significant associations were found for vitamin A and glutamine with intestinal barrier function.
Singh et al., 2014	Evaluate the effect of oral glutamine supplementation on intestinal permeability and endotoxemia in patients with severe acute pancreatitis	Glutamine	Oral	Patients with severe acute pancreatitis	7 days	There was no change in intestinal permeability after the intervention. EndoCab IgM increased significantly (P=0.0164) and C-reactive protein levels decreased.
Lima et al., 2014	Determine the impact of zinc, vitamin A and glutamine supplementation alone or in combination on growth, intestinal barrier function, stress and satiety-related hormones in Brazilian children from slums with low median height-to-age z-scores.	Glutamine alone (daily dose 16g); glutamine plus vitamin A plus zinc; and placebo (zinc vehicle plus vitamin A) plus glycine (glutamine isonitrogenic),	Oral	Children	1 year	Improvement of the intestinal barrier Improvement of z weight score for age and weight for height Plasma leptin was negatively correlated with

						plasma glutamine levels
de Souza et al., 2015	Determine whether oral supplementation with L-glutamine modifies the composition of the intestinal microbiota in overweight and obese adults.	L-alanine or L-glutamine: 30g/day	Oral	Obese and overweight adults	14 days	Oral glutamine supplementation for a short period of time altered the composition of the intestinal microbiota in overweight and obese humans, reducing the Firmicutes ratio for Bacteroidetes, which is similar to weight loss programs already seen in the literature.
Serrano-Villaret al., 2016	To evaluate the influence of glutamine supplementation in patients with rectal cancer undergoing preoperative radiochemotherapy.	Glutamine: 30g/day	Oral	Patients with rectal cancer undergoing preoperative radiochemotherapy.	5 weeks	There was no difference between the groups in the frequency and severity of diarrhea during radiochemotherapy (p = 0.5), insulin levels increased significantly in both groups, IL-6 only in the glutamine group.
Arutla et al., 2019	Evaluate the effect of enteral glutamine supplementation on clinical outcomes, intestinal permeability, systemic inflammation, oxidative stress, and plasma glutamine levels in patients with predicted severe acute pancreatitis.	Glutamine: 0.57 g/kg body weight per day	Enteral route	Patients with severe acute pancreatitis	7 days	Despite the absence of improvement in infected necrosis and in-hospital mortality, enteral glutamine supplementation showed improvement in intestinal permeability, oxidative stress and a tendency to improve organ function, as described by the improvement in the Modified Marshall score.

Moore et al., 2021	Determine the minimum dosage of alanil-glutamine needed to improve intestinal integrity and growth in children at risk of environmental enteropathy	Alanil-glutamine: 3g/day, 6g/day, 12 g/day	Oral Route	Children at risk of environmental enteropathy between 2 and 6 years	10 days of supplementation and 120 days of follow-up	The intermediate dose alanil-glutamine promotes short-term improvement in intestinal integrity and weight growth in children at risk of environmental enteropathy.
Ogden et al., 2022	Evaluate supplementation tolerance	L-glutamine: 3g/day, 6g/day, 9g/day	Oral Route	Healthy adult men	Acute dose	Acute oral intake of L-glutamine at dosages up to 0.9Hg/kg were generally well tolerated

The studies evaluated in this review address different dosages, intervention time and audiences. The heterogeneity of the studies allows the evaluation of glutamine supplementation in different realities, which may be an innovative and important review to evaluate the effects of this amino acid in clinical cases.

The work of Mitter et al. (2012) found positive associations with the use of 16g/day of glutamine in a population of 214 children at nutritional risk in Brazilian slums. At work, supplementation and follow-up for one year had the combined supplementation of vitamin A and Zinc. Half of the children received glutamine and the other did not. The results showed that vitamin A and glutamine improved intestinal barrier function and children with apolipoprotein E4(+) (a critical carrier protein involved in lipid homeotase) who received glutamine showed significant positive correlations between the change in height-to-age z scores over four months and delay in verbal learning, along with changes correlated over the same period in the z weight-for-age scores and z-scores of weight to height associated with nonverbal intelligence quotients.[10]

Singh et al. (2014) supplemented glutamine or placebo in patients with severe acute pancreatitis for 7 days. In the study, intestinal permeability was evaluated by excretion of lactulose/mannitol in urine and endotoxemia evaluated by essential antibodies of IgG and IgM endotoxin (EndoCab IgG and IgM), and the results showed that there was no change in intestinal permeability after the intervention. However, EndoCab IgM levels increased significantly

(P=0.0164) and C-reactive protein levels decreased significantly (P = 0.0236) in the group that received glutamine supplementation. No difference was observed in infectious complications, prealbumin value, hospitalization/intensive care unit and mortality in both groups.[11]

Glutamine supplementation was positive in alone or combined with vitamin A and zinc in 120 children after one year. The results of Lima et al. (2014) showed that glutamine treatment significantly improved weight-to-height z-scores compared to placebo-glycine control treatment. Glutamine alone or all the combined nutrients prevented disruption of intestinal barrier function, as measured by the percentage of urinary excretion of lactulose and the absorption ratio of lactulose:mannitol. In the study, plasma leptin was negatively correlated with plasma levels of glutamine (p = 0.002) and arginine (p = 0.001) at baseline. After glutamine treatment, leptin was correlated with z scores weight for age and weight for height (p≤0.002) at a 4-month follow-up. In addition, glutamine and all the combined nutrients (glutamine, vitamin A and zinc) improved intestinal barrier function in these children.[12]

De Souza et al. (2015) evaluated the effect of oral supplementation of 30 g of L-alanine (control) or 30 g of L-glutamine daily for 14 days in overweight or obese adults. Glutamine supplementation showed statistically significant differences in phylums of intestinal bacteria Firmicutes and Actinobacteria compared to those in the control group, and the proportion of Firmicutes for Bacteroidetes, a good biomarker for obesity, decreased in the glutamine group from 0.85 to 0.57, while increasing from 0.91 to 1.12 in the control group. At the gender level, Dialister, Dorea, Pseudobutyrivibrio and Veillonella, belonging to the phylum Firmicutes, had a statistically significant reduction. Positive results were observed, since, for a short period of time, glutamine supplementation altered the composition of the intestinal microbiota in overweight and obese humans reducing the Firmicutes ratio for Bacteroidetes, which is similar to weight loss programs already seen in the literature.[13]

Further studies evaluating the bacterial profile after glutamine supplementation are necessary, since the mechanisms proposed for this improvement are described in the literature and the real clinical effects need to be further studied.

When evaluating the supplementation of 30g/day of glutamine or placebo (maltodextrin), orally, for five weeks, in 33 patients with rectal cancer submitted to preoperative radioquimioterapia, Serrano-Villaret et al. (2016) found no difference between the groups in the frequency and severity of diarrhea during radiochemotherapy (p = 0.5). It was also seen that insulin levels increased significantly in both groups and IL-6 only in the glutamine group.[14]

Arutla et al. (2019) evaluated the effect of enteral glutamine supplementation on clinical results, intestinal permeability,

systemic inflammation, oxidative stress and plasma glutamine levels in patients with predicted severe acute pancreatitis. The study consisted of 18 patients admitted within 72 hours of symptom onset and 22 controls. Patients in the glutamine group received enteral glutamine supplementation of 0.57 g/kg of body weight per day, as a divided dosage throughout the day, in addition to the diet pattern. The results showed that there was no significant improvement in the development of infected necrosis and hospital mortality among the groups. There was improvement in the Modified Marshall score in a higher proportion of patients who received glutamine ($p = 0.05$) and plasma glutamine levels improved more in the glutamine-treated group ($p = 0.004$). A statistically significant reduction in IL-6 concentration was observed in the glutamine group at the end of treatment ($p = 0.02$).[14]

Moore et al. (2021) determined the minimum alanil-glutamine dosage needed to improve intestinal integrity and growth in children at risk of environmental enteropathy. The study obtained a sample of 140 children between 2 and 6 years of age. Oral supplementation of 10-day alanil glutamine was divided into three groups: 3g/day, 6g/day, 12 g/day, or an isonitrogenous dose of glycine placebo at 12.5g/day. In the group that received the highest dose, a modest improvement in urinary excretion of lactulose was detected from 0.19% on day 1 to 0.17% on day 10 ($P = 0.05$). There were significant but transient improvements in weight to weight and weight for height. The intermediate dose alanil-glutamine promotes short-term improvement in intestinal integrity and weight growth in children at risk of environmental enteropathy.[5]

Although glutamine is a suggestion of supplementation at the time of recovery of the intestinal flora, it is important to take into account the symptoms presented by the patient. Discomfort, nausea and flatulence are gastrointestinal symptoms that the patient who presents with digestive tract alterations already has, and in some studies, glutamine seems to be responsible for them, which should be taken into account at the time of supplementation.

Ogden et al. (2022) conducted a study to evaluate the effects of different doses of L-glutamine. The sample was characterized by fourteen healthy adult men (25±5 years old), who ingested different doses of L-glutamine: 0.3 (low dose), 0.6 (median dose) or 0.9 (high dosage) g/kg. Gastrointestinal symptoms up to 24 hours after intake of supplementation were higher in high dosage (0.9g/kg) compared to other doses used ($p < 0.05$). However, the severity of mild gastrointestinal symptoms seemed dose-dependent.[4]

Conclusion

The scientific findings on the subject do not yet have an exact conclusion. Although glutamine favors intestinal health, by mechanisms already elucidated, the dose for each pathology and

clinical parameter seems to differentiate, based on the results obtained and also on side effects.

Each patient is unique, and the complexity of the signs and symptoms should be considered at the time of choosing the dosage of glutamine supplementation.

Further research is suggested to elucidate the dosages, side effects and therapeutic responses of glutamine on intestinal health parameters.

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