



POINT OF VIEW

Glutamine and sickle cell disease in Brazilian scenario

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Background

Amino acids are organic molecules that possess, such as every amino acid, a carbon atom attached to a carboxyl group, an amino group, hydrogen, and a group called R, that could present a variable structure depending on the type of amino acid ^{1,2}.

It is already established that amino acids play important biological roles especially because they constitute the basic structural units of proteins ².

A type of amino acid that has attracted attention in recent years in the field of hematology, more specifically in the treatment of people with sickle cell disease (SCD) is glutamine ³.

Glutamine

Glutamine is an α -amino acid formed of butyric acid bearing an amino substituent at stance two and a carbamoyl substituent at stance four and has the molecular formula of $C_5H_{10}N_2O_3$ ⁴ (Figure 1). There are two glutamine isomer types, L-Glutamine: frequent in foods and dietary supplements, and D-glutamine; an enantiomer of L-glutamine, frequent in microorganisms such as bacteria ⁵⁻⁷.

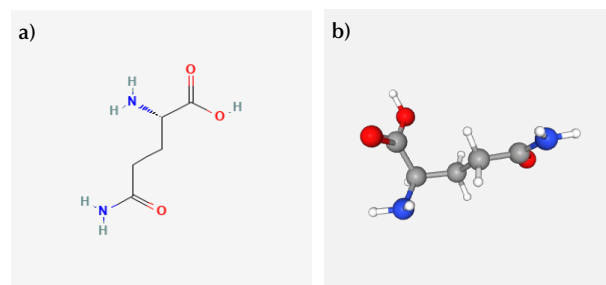


Figure 1. Molecular structures of glutamine. a) Structure in two dimensions (2-D). b) Structure in three dimensions (3-D) ⁴

Glutamine or L-glutamine is a conditionally essential amino acid, and it is a precursor of some conditionally essential amino acids ^{2,8}. Glutamine is synthesized from glutamic acid and ammonia, it is an important nitrogen transporter in the body and a source of energy for cells ^{9,10}.

L-glutamine, present in abundance throughout the body, is involved in several metabolic processes, and, therefore, becomes essential in pathologies that involve intense

catabolism, or even in intense exercise, due to the greater metabolic demand in several diseases ^{2, 11-13}.

Among the roles played by glutamine, is its participation as a substrate for protein synthesis, for urogenesis in the liver and hepatic and renal gluconeogenesis; being a precursor of anabolics for muscle growth. Furthermore, glutamine participates in the synthesis of neurotransmitters and nucleic acids, from nucleotides, in the production of glutathione and in the regulation of acid-base balance in the kidney. In addition, this amino acid is an oxidative fuel in the gut and immune system cells and can be involved in the provision of nitrogen transport between organs ^{12, 13}.

Glutamine plays a fundamental role in various types of disorders and diseases. In cardiovascular diseases, for example, it drives crucial processes in vascular cells such as external cells, apoptosis, senescence, and extracellular matrix deposition, as well as protecting against cardiometabolic diseases such as obesity, diabetes, and dyslipidemia ¹⁴. Cancerogenous cells depend on the supply of glutamine for your metabolism and growth, so several strategies to inhibit its supply are used in cancer therapy ¹⁵. An example of this is the use of L-asparaginases in the treatment of patients ALL, through the deamidation reaction of both asparagine and glutamine, to generate the depletion of these amino acids ¹⁵. For memory, glutamine is necessary for physiological synaptic activity and memory to promote cognitive processes ^{16, 17}.

Glutamine can also be found in animal and plant sources. This amino acid is usually measured by the amount of glutamate in the food, as it is produced through the conversion of glutamic acid with the participation of ammonia, primarily by skeletal muscle and the liver ^{18, 19}. Therefore, in the form of glutamate, it is generally present in milk, cheese, yogurt, legumes (chickpeas, beans, lentils), beets, spinach, yellow corn, and tofu ^{18, 19}. The production of glutamine at the industrial scale can be used to produce the amino acid as an additive, supplement, or pharmaceutical product ²⁰.

Glutamine supplementation has been well documented in the literature for various purposes such as the treatment of diseases associated with dysbiosis ²¹, ergogenic effect for athletes ²², premature infants through enteral diet ²³, low birth weight newborns, and children with serious illnesses ²⁴. The parenteral administration of glutamine has been used in various conditions that lead to metabolic stress such as dengue, HIV, and, until burn ². Glutamine supplementation in increased amounts for a short period to correct cases of deficiency has been considered safe ^{25, 26}. However, its long-term supplementation in large amounts (~40 g/d) ²⁶ has been questioned for possibly leading to metabolic alterations that can trigger negative effects on the human body (Table 1).

In Brazil, Resolution number 656 of June 15, 2020, of the Federal Council of Nutritionists regulates the dietary prescription of nutritional supplements such as L-glutamine, as part of the nutritionist's attributions ²⁷.

Table 1. Some of the possible negative effects of high-dose supplementation and chronic glutamine use

Changes	Possible Effects
Transport of amino acids	<ul style="list-style-type: none"> - Impairs the distribution of amino acids between tissues and their absorption in the intestine and kidneys
Glutamine GLN metabolism	<ul style="list-style-type: none"> - Impaired endogenous glutamine synthesis - ↑ in the production of glutamate and ammonia
Ammonia transport	<ul style="list-style-type: none"> - Impairments in ammonia detoxification - Affecting glutamine's role as an ammonia transporter between tissues
Abnormalities in aminoacidemia	<ul style="list-style-type: none"> - ↑ of the plasmatic levels of glutamine, glutamate, citrulline, ornithine, arginine, and histidine - ↓ of the levels of valine, leucine, isoleucine, glycine, threonine, serine, and proline
Effect of glutamine supplementation withdrawal	<ul style="list-style-type: none"> - Due to the body's adaptive response to ↑ glutamine consumption, its withdrawal may ↑ risk health problems resulting from glutamine deficiency

Adapted from Holecck ²⁶

Sickle cell disease

SCD is a type of structural and genetic hemoglobinopathy characterized by the appearance of a variant of hemoglobin A called sickle cell hemoglobin (HbS) ²⁸⁻³⁰.

The main primary events that act in the pathophysiology of SCD are the vaso-occlusion of the bloodstream and the early destruction of erythrocytes, tissue ischemia, anemia, inflammation, and oxidative stress. These can lead to several complications secondary to the disease, including acute and chronic pain, cardiopulmonary disease, central nervous system disease and kidney disease ³¹⁻³⁴. Among other complications are constant infections, splenic sequestration, acute chest syndrome, stroke, leg ulcer, and the progression of multiple organ degeneration ³¹⁻³⁴.

Acute and chronic complications in individuals with SCD have clinical, hematological, and metabolic outcomes that can affect their energy requirements^{35,36}, body composition³⁷, as well as the quality of life³⁸⁻⁴⁰.

Glutamine in the international scenario

Over time, several therapies have been used to treat SCD. Some studies indicate the main therapies that can change the course of the most severe genotype of SCD, called sickle cell anemia (Hb SS). These therapies are hydroxyurea, hydroxycarbamide, red blood cell transfusion, and hematopoietic stem cell transplantation^{31,41,42}.

However, further innovative therapies have been studied and have shown promising results as alternatives or supplements to standard treatments, including voxelotor, crizanlizumab, and L-glutamine^{31,41,42}.

The considerable explosion of knowledge generated about the role of glutamine in SCD is related to the reduction of oxidative stress through increased levels of NADH (nicotinamide adenine dinucleotides + hydrogen), to reduce the acute events caused by painful crises in patients^{3,31,33,43,44}.

One of the main studies that proved the effectiveness of the use of glutamine in patients with SCD was the study undertaken by Niihara et al.⁴⁵ called *A Phase 3 Trial of L-Glutamine in Sickle Cell Disease*, published in *The New England Journal of Medicine* in August 2018. The authors of this article supported that oxidative stress would contribute to the complex pathophysiology of SCD and that it should be diminished by decreasing nicotinamide adenine dinucleotides (NAD⁺) through glutamine supplementation to reduce pain episodes⁴⁵.

This multicenter, randomized, placebo-controlled, double-blind, phase 3 study tested the effectiveness of L-glutamine (0.3 g per kilogram of body weight per dose) administered twice daily orally, compared with placebo, in reducing the incidence of pain crises in patients with sickle cell disease (HbSS genotype) or sickle cell disease β^0 -thalassemia (HbS β^0 tal genotype) with a history of two or more pain crises in the previous year⁴⁵.

As described in the study, 230 patients aged 5 – 58 years (53.9 % female) were randomly assigned, in a 2:1 ratio, to receive either L-glutamine (152 patients) or placebo (78 patients)⁴⁵. As a result, patients in the L-glutamine group had significantly fewer pain flare-ups and fewer hospitalizations than those in the placebo group⁴⁵. The major issue outlined in the article was that two-thirds of patients, in both trial groups received hydroxyurea concomitantly⁴⁵ and those adverse effects such as low-grade nausea, non-cardiac chest pain, fatigue, and musculoskeletal pain occurred more frequently in the L-glutamine group than in the placebo group⁴⁵.

The study carried out by Niihara et al.⁴⁵ concluded that among children and adults with HbSS, the average number of pain attacks over 48 weeks was lower among those who received oral L-glutamine therapy, administered alone or with hydroxyurea, than among those who received oral L-glutamine therapy, either alone or with hydroxyurea and those who received a placebo, with or without hydroxyurea.

One more study demonstrated the action of glutamine in the regulation of apoptosis and autophagy markers in peripheral blood mononuclear cells in SCD⁴⁶. The authors evaluated the Bcl-2-associated X protein 4, also known as the mitochondrial BAX protein being involved in the regulation of the intrinsic active cell death of leukocytes and also studied autophagy, a mechanism responsible for the renewal of organelles and macromolecules using the pathway of lysosomal degradation⁴⁶. These two markers could have dysfunction in pulmonary hypertension in SCD and glutamine could help by acting in the regulation of leukocyte metabolism^{7,47,48}.

The same authors completed an 8-week prospective phase 2 study supplementing 10 g (TID) of L-glutamine via the oral route in 8 patients at risk of developing pulmonary hypertension. As a result, they observed a 300 % increase in BAX expression and a significant increase in the LC3-II/LC3-I ratio, indicating that supplementation possibly provided a positive regulation of apoptosis and autophagy by proteins in SCD⁴⁶.

Glutamine and SCD in the current Brazilian scenario

In July 2017, the U.S. Food and Drug Administration (FDA) approved the use of glutamine in the L-glutamine form for oral administration for the reduction of HbSS acute complications, the most severe genotype of the disease, in patients over 5 years of age^{49,50}. Despite this, to date, approval of L-glutamine for SCD by the European Medicines Agency (EMA) has not been identified^{51,52}.

In the Brazilian scenario, despite a study mentioning that the National Health Surveillance Agency (ANVISA) was starting the process of recommending the use of glutamine in Brazil¹⁹, no official information was revealed from ANVISA regarding approval of the use of L-glutamine by SCD patients in Brazil⁵³⁻⁵⁵.

The drug therapy that was recently approved in Brazil was the use of crizanlizumab^{51,56,57} from Novartis⁵³ for the prevention of vaso-occlusive crises (CVOs) in patients with SCD.

Although there is no approval and incorporation of L-glutamine in the Unified Health System (SUS) to date, the Ministry of Health has recently (October 20, 2022) released through its news website the publication of the Technological Horizon Monitoring (MHT) report on medicines for the

treatment of SCD prepared by the National Commission for the Incorporation of Technologies in the SUS (CONITEC) ^{52, 58}. The objective of the document would be to address new technologies with studies on different medicines and their potential impact on the SUS.

The document recognizes that L-glutamine is approved by an international regulatory agency (FDA) and that it could bring benefits in reducing pain crises and increasing hemoglobin levels. Despite this, as well as the FDA, EMA, and the CONITEC document report have identified some limitations in the scientific studies analyzed, such as a reduced number of patients, lack of randomization, and blinding, among others ^{52, 58}.

Conclusion

It is undeniable that L-glutamine can bring survival benefits to patients with SCD by balancing the NAD⁺/NADH ratio ^{59, 60} to decrease CVOs in patients with SCDD ⁵¹. It is known that the survival of patients with SCD in first-world countries such as the USA and England can reach ages over 60 years which cannot be compared with data from some national studies in Brazilian capitals that indicate that the median mortality would be around 30 years ⁶¹⁻⁶³.

Even with the approval of crizanlizumab, L-glutamine remains an option to be studied in the long term for use in Brazilian patients with SCD. It is hoped that international and national regulatory agencies will be able to jointly assess the role of L-glutamine to declare a unified opinion regarding this technology.

For national organizations such as the Brazilian Association of Food and Nutrition (ASBRAN) and CFN (Federal Council of Nutritionists), the mission is to issue opinions on the subject to bring more clarification on the benefits of glutamine in individuals with SCD.

For us as Nutritionists, there will be an opportunity to reflect on how L-glutamine can act not only in reducing CVOs but also in dysbiosis ⁶⁴⁻⁶⁶ since it could be present in patients with SCD ⁶⁷⁻⁷⁰.

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