Nor. Afr. J. Food Nutr. Res. 2023; 7 (15): 43-51

https://doi.org/10.51745/najfnr.7.15.43-51

https://www.najfnr.com

POINT OF VIEW

Glutamine and sickle cell disease in Brazilian scenario

Karen Cordovil *

Oswaldo Cruz Foundation, Sergio Arouca National School of Public Health, Postgraduate Epidemiology Program in Public Health, Leopoldo Bulhões street, 1480 - Manguinhos, Rio de Janeiro, Brazil

ARTICLE INFORMATION

* **Corresponding author:** Karen Cordovil. Tel. + 55 87 38829208 or +55 21 987166331. E-mail: karensouz@gmail.com

Received: October 30, 2022
Revised: February 24, 2023
Accepted: February 27, 2023
Published: March 01, 2023

Article edited by:
- Pr. Meghit Boumediene Khaled

Article reviewed by:
- Pr. Amina Chentouf
- Dr. Nihada Ahmetovic

Cite this article as: Codovil, K. (2023). Glutamine and sickle cell disease in Brazilian scenario. *The North African Journal of Food and Nutrition Research, 7* (15): 43-51. https://doi.org/10.51745/najfnr.7.15.43-51

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].

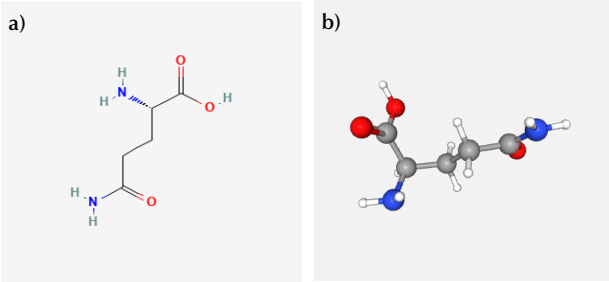

Figure 1. Molecular structures of glutamine. a) Structure in two dimensions (2-D). b) Structure in three dimensions (3-D) [4]

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	- Impairs the distribution of amino acids between tissues and their absorption in the intestine and kidneys
Glutamine GLN metabolism	- Impaired endogenous glutamine synthesis - ↑ in the production of glutamate and ammonia
Ammonia transport	- Impairments in ammonia detoxification - Affecting glutamine's role as an ammonia transporter between tissues
Abnormalities in aminoacidemia	- ↑ 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	- Due to the body's adaptive response to ↑ glutamine consumption, its withdrawal may ↑ risk health problems resulting from glutamine deficiency

Adapted from Holecek [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 composition [37], as well as the quality of life [38-40].

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 episodes [45].

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 (HbSβ^0tal genotype) with a history of two or more pain crises in the previous year [45].

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 group [45]. The major issue outlined in the article was that two-thirds of patients, in both trial groups received hydroxyurea concomitantly [45] 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 group [45].

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 SCD [46]. 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 degradation [46]. 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 SCD [46].

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 Brazil [19], no official information was revealed from ANVISA regarding approval of the use of L-glutamine by SCD patients in Brazil [53-55].

The drug therapy that was recently approved in Brazil was the use of crizanlizumab [51, 56, 57] from Novartis [53] 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].

Author Contribution: K.C. contributed with all study conception and writing.

Acknowledgment (if applicable): The authors acknowledged the permission granted by the administrators of the Islamic and Arabic schools where this study was conducted.

Funding (financial support): Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) - Financing Code 001.

Previous presentations: The manuscript has not been presented as part of a meeting, the organization, or the place.

Conflicts of Interest: The author declare that there isn't a potential conflict of interest, including political and/or financial interests associated with patents or ownership, provision of materials and/or inputs, and equipment used in the study by the manufacturers.

References

[1] Cuppari L. Guias de Medicina Ambulatorial e Hospitalar da EPM-UNIFESP. Barueri (Ed.). (2014). *Guias de Medicina Ambulatorial e Hospitalar da EPM-UNIFESP*. *578*.

[2] Cruzat, V. F., Petry, É. R., & Tirapegui, J. (2009). Glutamina: aspectos bioquímicos, metabólicos, moleculares e suplementação. *Revista Brasileira de Medicina Do Esporte*, *15*(5), 392–397. https://doi.org/10.1590/s1517-86922009000600015

[3] Wu, H.-W., Gannon, M., & Hsu, L. L. (2023). Evaluation of glutamine utilization in patients with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *45*(1), e52–e55. https://doi.org/10.1097/MPH.0000000000002519

[4] PubChem. (n.d.). *DL-Glutamine*. Nih.gov. Retrieved February 10, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/DL-Glutamine

[5] PubChem. (n.d.). *D-glutamine*. Nih.gov. Retrieved February 10, 2023, from https://pubchem.ncbi.nlm.nih.gov/compound/D-glutamine

[6] Brown, G., Singer, A., Proudfoot, M., Skarina, T., Kim, Y., Chang, C., Dementieva, I., Kuznetsova, E., Gonzalez, C. F., Joachimiak, A., Savchenko, A., & Yakunin, A. F. (2008). Functional and structural characterization of four glutaminases from Escherichia coli and Bacillus subtilis. *Biochemistry*, *47*(21), 5724–5735. https://doi.org/10.1021/bi800097h

[7] Cruzat, V., Macedo Rogero, M., Noel Keane, K., Curi, R., & Newsholme, P. (2018). Glutamine: Metabolism and immune function, supplementation and clinical translation. In *Preprints*. https://doi.org/10.20944/preprints201809.0459.v1

[8] Newsholme, E. A., Crabtree, B., & Ardawi, M. S. (1985). Glutamine metabolism in lymphocytes: Its biochemical, physiological and clinical importance. *Quarterly Journal of Experimental*

Physiology, *70*(4), 473-489. https://doi.org/10.1113/expphysiol.1985.sp002935

[9] Yoo, H. C., Yu, Y. C., Sung, Y., & Han, J. M. (2020). Glutamine reliance in cell metabolism. *Experimental & Molecular Medicine*, *52*(9), 1496-1516. https://doi.org/10.1038/s12276-020-00504-8

[10] Dmitriev, A., Machulina, I., & Shestopalov, A. (2021). Glutamine as a component of nutritional and metabolic therapy for surgical patients in ICU. *Khirurgiya. Zhurnal im. N.I. Pirogova*, (8), 98. https://doi.org/10.17116/hirurgia202108198

[11] Severo, J. S., Da Silva Barros, V. J., Alves da Silva, A. C., Luz Parente, J. M., Lima, M. M., Moreira Lima, A. Â., Dos Santos, A. A., Matos Neto, E. M., & Tolentino, M. (2021). Effects of glutamine supplementation on inflammatory bowel disease: A systematic review of clinical trials. *Clinical Nutrition ESPEN*, *42*, 53-60. https://doi.org/10.1016/j.clnesp.2020.12.023

[12] Martins, P. (2016). Glutamine in critically ill patients: is it a fundamental nutritional supplement? *Revista Brasileira de Terapia Intensiva*, *28* (2), 100-103. https://doi.org/10.5935/0103-507X.20160022

[13] Martins, P. A. (2008). *Resposta imunitária em ratos suplementados com óleo de peixe e glutamina, treinados durante seis semanas*. https://acervodigital.ufpr.br/handle/1884/16093

[14] Durante, W. (2019). The emerging role of L-GLutamine in cardiovascular health and disease. *Nutrients*, *11*(9), 2092. https://doi.org/10.3390/nu11092092

[15] Cluntun, A. A., Lukey, M. J., Cerione, R. A., & Locasale, J. W. (2017). Glutamine metabolism in cancer: Understanding the heterogeneity. *Trends in Cancer*, *3*(3), 169-180. https://doi.org/10.1016/j.trecan.2017.01.005

[16] Bakoyiannis, I. (2022). Role of astroglial glutamine in memory. *Lab Animal*, *51*(4), 99-99. https://doi.org/10.1038/s41684-022-00954-9

[17] Cheung, G., Bataveljic, D., Visser, J., Kumar, N., Moulard, J., Dallérac, G., Mozheiko, D., Rollenhagen, A., Ezan, P., Mongin, C., Chever, O., Bemelmans, A., Lübke, J., Leray, I., & Rouach, N. (2022). Physiological synaptic activity and recognition memory require astroglial glutamine. *Nature Communications*, *13*(1). https://doi.org/10.1038/s41467-022-28331-7

[18] Talbott, S. M., & Hughes, K. (2008). *Suplementos Dietéticos Para Profissionais de Saúde. 1a edição. Editora Guanabara Koogan*

[19] Dantas Moraes Freire, M., Bezerra Lucas das Chagas, N. M., Queiroz dos Santos, S., Menezes Freire, S., & Menezes Freire, A. N. (2020). Aspectos Biológicos Da L-glutamina: Iimunomodulação E Hipertrofia muscular – Estudo AO Longo do tempo. *Revista Científica Hospital Santa Izabel*, *4*(1), 32-47. https://doi.org/10.35753/rchsi.v4i1.70

[20] Kusumoto, I. (2001). Industrial production of L-glutamine. *The Journal of Nutrition*, *131*(9), 2552S-2555S. https://doi.org/10.1093/jn/131.9.2552s

[21] Gelisk Pereira, I., & Rodrigues Ferraz, I. A. (2017). Suplementação de glutamina no tratamento de doenças associadas a disbiose intestinal. *Revista Brasileira de Saúde Funcional*, *5*(1), 46. https://doi.org/10.25194/rebrasf.v5i1.830

[22] Fontana, K. E., Valdes, H., & Baldissera, V. (2003). Glutamina como suplemento ergogênico. *Revista Brasileira de Ciência e Movimento*, *11*(3), 85–90.

[23] Borges, M. C., Rogero, M. M., & Tirapegui, J. (2008). Suplementação enteral E parenteral com glutamina Em neonatos pré-termo E com baixo peso AO nascer. *Revista Brasileira de Ciências Farmacêuticas*, *44*(1), 13-23. https://doi.org/10.1590/s1516-93322008000100003

[24] Pacífico, S. L., Leite, H. P., & Carvalho, W. B. (2005). A suplementação de glutamina E benéfica Em crianças com doenças Graves? *Revista de Nutrição*, *18*(1), 95-104. https://doi.org/10.1590/s1415-52732005000100009

[25] Nienaber, A., Dolman, R. C., Van Graan, A. E., & Blaauw, R. (2015). Prevalence of glutamine deficiency in ICU patients: A cross-sectional analytical study. *Nutrition Journal*, *15*(1). https://doi.org/10.1186/s12937-016-0188-3

[26] Holecek, M. (2012). Side effects of long-term glutamine supplementation. *Journal of Parenteral and Enteral Nutrition*, *37*(5), 607-616. https://doi.org/10.1177/0148607112460682

[27] Brasil. Resolução CFN nº 656 de 15 de junho de 2020. Dispõe sobre a prescrição dietética, pelo nutricionista, de suplementos alimentares e dá outras providências. [Internet]. 656 2018. Available from: https://www.in.gov.br/en/web/dou/-/resolucao-n-656-de-15-de-junho-de-2020-262145306

[28] Esrick, E. B., Lehmann, L. E., Biffi, A., Achebe, M., Brendel, C., Ciuculescu, M. F., Daley, H., MacKinnon, B., Morris, E., Federico, A., Abriss, D., Boardman, K., Khelladi, R., Shaw, K., Negre, H., Negre, O., Nikiforow, S., Ritz, J., Pai, S., … Williams, D. A. (2021). Post-transcriptional genetic silencing of*BCL11A*to treat sickle cell disease. *New England Journal of Medicine*, *384*(3), 205-215. https://doi.org/10.1056/nejmoa2029392

[29] Demirci, S., Uchida, N., & Tisdale, J. F. (2018). Gene therapy for sickle cell disease: An update. *Cytotherapy*, *20*(7), 899-910. https://doi.org/10.1016/j.jcyt.2018.04.003

[30] Park, S. H., & Bao, G. (2021). CRISPR/Cas9 gene editing for curing sickle cell disease. *Transfusion and Apheresis Science*, *60*(1), 103060. https://doi.org/10.1016/j.transci.2021.103060

[31] Kato, G. J., Piel, F. B., Reid, C. D., Gaston, M. H., Ohene-Frempong, K., Krishnamurti, L., Smith, W. R., Panepinto, J. A., Weatherall, D. J., Costa, F. F., & Vichinsky, E. P. (2018). Sickle cell disease. *Nature Reviews Disease Primers*, *4*(1). https://doi.org/10.1038/nrdp.2018.10

[32] Karafin, M. S., Koch, K. L., Rankin, A. B., Nischik, D., Rahhal, G., Simpson, P., & Field, J. J. (2015). Erythropoietic drive is the strongest predictor of hepcidin level in adults with sickle cell disease. *Blood Cells, Molecules, and Diseases*, *55*(4), 304-307. https://doi.org/10.1016/j.bcmd.2015.07.010

[33] Nur, E., Biemond, B. J., Otten, H., Brandjes, D. P., & Schnog, J. B. (2011). Oxidative stress in sickle cell disease; pathophysiology and potential implications for disease management. *American Journal of Hematology*, *86*(6), 484-489. https://doi.org/10.1002/ajh.22012

[34] Ferrão, T. D., Martins-Filho, P. R., Aragão, C., Santana, M., Nascimento, A., Cardoso, T., & Cipolotti, R. (2017). Doppler velocimetry of the orbital arteries in patients with sickle cell anemia: Relationship with biomarkers of hemolysis. *Radiologia Brasileira*, *50*(2), 103-108. https://doi.org/10.1590/0100-3984.2015.0180

[35] Souza, K. C., Araújo, P. I., Souza-Junior, P. R., & Lacerda, E. M. (2011). Baixa estatura E magreza Em crianças E adolescentes com doença falciforme. *Revista de Nutrição*, *24*(6), 853-862. https://doi.org/10.1590/s1415-52732011000600006

[36] Cordovil, K., Crivelli, M., Calixto Lima, L., S. Barbosa, F., & Fleury, M. (2022). Predictive equations overestimated the rest energy expenditure by indirect calorimetry in adults with sickle cell disease. *The North African Journal of Food and Nutrition Research*, *6*(14), 94-106. https://doi.org/10.51745/najfnr.6.14.94-106

[37] Cordovil, K., Crivelli, M., Brito, F. D., & Fleury, M. (2022). Body composition, energy expenditure, and markers of hemolysis in adults with sickle cell disease. *The North African Journal of Food and Nutrition Research*, *6*(13), 55-65. https://doi.org/10.51745/najfnr.6.13.55-65

[38] Jaouni, S. A., Muhayawi, M. A., & Halawa, T. (2012). PO23 health and quality of life outcomes in patient with sickle cell disease. *Critical Reviews in Oncology/Hematology*, *82*, S17. https://doi.org/10.1016/s1040-8428(12)70037-9

[39] Freitas, S. L., Ivo, M. L., Figueiredo, M. S., Gerk, M. A., Nunes, C. B., & Monteiro, F. D. (2018). Quality of life in adults with sickle cell disease: An integrative review of the literature. *Revista Brasileira de Enfermagem*, *71*(1), 195-205. https://doi.org/10.1590/0034-7167-2016-0409

[40] Gomes, L. M., Vieira, M. M., Reis, T. C., Barbosa, T. L., & Caldeira, A. P. (2011). Knowledge of family health program practitioners in Brazil about sickle cell disease: A descriptive, cross-sectional study. *BMC Family Practice*, *12*(1). https://doi.org/10.1186/1471-2296-12-89

[41] Brandow, A. M., & Liem, R. I. (2022). Advances in the diagnosis and treatment of sickle cell disease. *Journal of Hematology &*

Oncology, *15*(1). https://doi.org/10.1186/s13045-022-01237-z

[42] Kassim, A. A., & DeBaun, M. R. (2014). The case for and against initiating either hydroxyurea therapy, blood transfusion therapy or hematopoietic stem cell transplant in asymptomatic children with sickle cell disease. *Expert Opinion on Pharmacotherapy*, *15*(3), 325-336. https://doi.org/10.1517/14656566.2014.868435

[43] Sadaf, A., & Quinn, C. T. (2020). L-glutamine for sickle cell disease: Knight or pawn? *Experimental Biology and Medicine*, *245*(2), 146-154. https://doi.org/10.1177/1535370219900637

[44] Cox, S., Hart, E., Kirkham, F., & Stotesbury, H. (2020). L-glutamine in sickle cell disease. *Drugs of Today*, *56*(4), 257. https://doi.org/10.1358/dot.2020.56.4.3110575

[45] Niihara, Y., Miller, S. T., Kanter, J., Lanzkron, S., Smith, W. R., Hsu, L. L., Gordeuk, V. R., Viswanathan, K., Sarnaik, S., Osunkwo, I., Guillaume, E., Sadanandan, S., Sieger, L., Lasky, J. L., Panosyan, E. H., Blake, O. A., New, T. N., Bellevue, R., Tran, L. T., … Vichinsky, E. P. (2018). A phase 3 trial of<scp>l</scp>-glutamine in sickle cell disease. *New England Journal of Medicine*, *379*(3), 226-235. https://doi.org/10.1056/nejmoa1715971

[46] Walter, P. B., Hohman, L. S., Rokeby, A., Lum, J. J., Hagar, R., Lavrisha, L., Saulys, A., Kuypers, F. A., Vichinsky, E., & Morris, C. R. (2022). The effects of glutamine supplementation on markers of apoptosis and autophagy in sickle cell disease peripheral blood mononuclear cells. *Complementary Therapies in Medicine*, *70*, 102856. https://doi.org/10.1016/j.ctim.2022.102856

[47] Marshall, J. D., Bazan, I., Zhang, Y., Fares, W. H., & Lee, P. J. (2018). Mitochondrial dysfunction and pulmonary hypertension: Cause, effect, or both. *American Journal of Physiology-Lung Cellular and Molecular Physiology*, *314*(5), L782-L796. https://doi.org/10.1152/ajplung.00331.2017

[48] Morris, C. R., Brown, L. A., Reynolds, M., Dampier, C. D., Lane, P. A., Watt, A., Kumari, P., Harris, F., Manoranjithan, S., Mendis, R. D., Figueroa, J., & Shiva, S. (2020). Impact of arginine therapy on mitochondrial function in children with sickle cell disease during vaso-occlusive pain. *Blood*, *136*(12), 1402-1406. https://doi.org/10.1182/blood.2019003672

[49] Center for Drug Evaluation, & Research. (n.d.). *FDA approved L-glutamine powder for the treatment of sickle cell disease*. U.S. Food and Drug Administration; FDA. Retrieved March 1, 2023, from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approved-l-glutamine-powder-treatment-sickle-cell-disease

[50] Wilmore, D. W. (2017). Food and Drug Administration approval of glutamine for sickle cell disease: Success and precautions in glutamine research. *Journal of Parenteral and Enteral Nutrition*, *41*(6), 912-917. https://doi.org/10.1177/0148607117727271

[51] Darbari, D. S., Sheehan, V. A., & Ballas, S. K. (2020). The vaso-occlusive pain crisis in sickle cell disease: Definition, pathophysiology, and management. *European Journal of Haematology*, *105*(3), 237-246. https://doi.org/10.1111/ejh.13430

[52] Brasil, Ministério da Saúde, Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde - CONITEC. Monitoramento do Horizonte Tecnológico (MHT) sobre medicamentos para o tratamento de Doença Falciforme. [Internet]. 2022. Available from: https://www.gov.br/conitec/pt-br/midias/radar/2022/20221011_mht_doenca-falciforme.pdf

[53] Brasil, Ministério da Saúde, Agência Nacional de Vigilância Sanitária - Anvisa. Medicamentos registrados para doencas raras [Internet]. Ministério da Saúde; 2021. Available from: https://www.gov.br/anvisa/pt-br/setorregulado/regularizacao/medicamentos/doencas-raras/medicamentos-registrados-para-doencas-raras

[54] Brasil, Ministério da Saúde, Agência Nacional de Vigilância Sanitária - Anvisa. Doenças raras: saiba mais sobre o registro de medicamentos [Internet]. Agência Nacional de Vigilância Sanitária - Anvisa. 2022 [cited 2022 Oct 21]. Available from: https://www.gov.br/anvisa/pt-br/assuntos/noticias-

anvisa/2022/doencas-raras-saiba-mais-sobre-o-registro-de-medicamentos

[55] Brasil, Ministério da Saúde, Agência Nacional de Vigilância Sanitária - Anvisa. Recorde de medicamentos aprovados para doenças raras - Notícias - Anvisa [Internet]. Agência Nacional de Vigilância Sanitária - Anvisa. 2020 [cited 2022 Oct 21]. Available from: http://antigo.anvisa.gov.br/en_US/noticias?=record-de-medicamentos-aprovados-para-doencas-raras&_101_INSTANCE_FXrpx9qY7FbU_struts_action=%2Fasset_publisher%2Fview_content&_101_INSTANCE_FXrpx9qY7FbU_assetEntryId=5795563&_101_INSTANCE_FXrpx9qY7FbU_type=content

[56] Thom, H., Jansen, J., Shafrin, J., Zhao, L., Joseph, G., Cheng, H., Gupta, S., & Shah, N. (2020). Crizanlizumab and comparators for adults with sickle cell disease: A systematic review and network meta-analysis. *BMJ Open*, *10*(9), e034147. https://doi.org/10.1136/bmjopen-2019-034147

[57] Sins, J. W., Mager, D. J., Davis, S. C., Biemond, B. J., & Fijnvandraat, K. (2017). Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: A systematic review. *Blood Advances*, *1*(19), 1598-1616. https://doi.org/10.1182/bloodadvances.2017007211

[58] Brasil, Ministério da Saúde, Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde -CONITEC. Ministério da Saúde divulga monitoramento de tecnologias para tratamento de doença falciforme [Internet]. Ministério da Saúde. 2022 [cited 2022 Oct 21]. Available from: https://www.gov.br/saude/pt-br/assuntos/noticias/2022/outubro/ministerio-da-saude-divulga-monitoramento-de-tecnologias-para-tratamento-de-doenca-falciforme

[59] Teodoro, J. S., Rolo, A. P., & Palmeira, C. M. (2013). The NAD ratio redox paradox: Why does too much reductive power cause oxidative stress? *Toxicology Mechanisms and Methods*, *23*(5), 297-302. https://doi.org/10.3109/15376516.2012.759305

[60] Yan, L., Wu, J., Jin, Z., & Zheng, H. (2016). Sources and implications of NADH/NAD+ redox imbalance in diabetes and its complications. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 145. https://doi.org/10.2147/dmso.s106087

[61] Dias, M. (1996). Mortalidade por doença falciforme no Brasil: estudo retrospectivo (1996 – 2016). *Academia Da Ciência e Tecnologia (AC&T)*, *1*.

[62] Araujo, O. M., Ivo, M. L., Ferreira Júnior, M. A., Pontes, E. R., Bispo, I. M., & Oliveira, E. C. (2015). Survival and mortality among users and non-users of hydroxyurea with sickle cell disease. *Revista Latino-Americana de Enfermagem*, *23*(1), 67-73. https://doi.org/10.1590/0104-1169.3385.2526

[63] Loureiro, M. M., & Rozenfeld, S. (2005). Epidemiology of sickle cell disease hospital admissions in Brazil. *Revista de saude publica*, *39*(6), 943–949. https://doi.org/10.1590/s0034-89102005000600012

[64] Bellocchi, C., Fernández-Ochoa, Á., Montanelli, G., Vigone, B., Santaniello, A., Milani, C., Quirantes-Piné, R., Borrás-Linares, I., Ventura, M., Segura-Carretero, A., Alarcón-Riquelme, M. E., & Beretta, L. (2018). Microbial and metabolic multi-omic correlations in systemic sclerosis patients. *Annals of the New York Academy of Sciences*, *1421*(1), 97-109. https://doi.org/10.1111/nyas.13736

[65] Viana dos Santos, R., Das Neves Ferreira, T., Oliveira de Almeida, D., Brito da Silva Fatal, L., & Queiroz Araujo, E. M. (2021). Nutrition management of Niemann pick disease type C: A case report. *Endocrine Regulations*, *55*(4), 238-241. https://doi.org/10.2478/enr-2021-0026

[66] Ohta T., Makino I., Okazaki M., Miyashita T., & Tajima H. (2021). Intestinal care using L−glutamine supplement and probiotics can induce a strong anti−tumor immune response through the induction of mature tertiary lymphoid structures in pancreatic cancer patients receiving preoperative chemotherapy. *Gan to kagaku ryoho. Cancer & Chemotherapy*, *48*(4), 465–471

[67] Brim, H., Taylor, J., Abbas, M., Vilmenay, K., Daremipouran, M., Varma, S., Lee, E., Pace, B., Song-Naba, W. L., Gupta, K., Nekhai, S., O'Neil, P., & Ashktorab, H. (2021). The gut microbiome in sickle cell disease: Characterization and potential implications. *PLOS ONE*, *16*(8), e0255956. https://doi.org/10.1371/journal.pone.0255956

[68] Stewart, C., Jang, T., Mo, G., Mohamed, N., Poplawska, M., Egini, O., Dutta, D., & Lim, S. H. (2021). Antibiotics to modify sickle cell disease vaso-occlusive crisis? *Blood Reviews*, *50*, 100867. https://doi.org/10.1016/j.blre.2021.100867

[69] Lim, S. H., Morris, A., Li, K., Fitch, A. C., Fast, L., Goldberg, L., Quesenberry, M., Sprinz, P., & Methé, B. (2018). Intestinal microbiome analysis revealed dysbiosis in sickle cell disease. *American Journal of Hematology*, *93*(4), E91-E93. https://doi.org/10.1002/ajh.25019

[70] Mohandas, S., Soma, V. L., Tran, T. D., Sodergren, E., Ambooken, T., Goldman, D. L., Weinstock, G., & Herold, B. C. (2020). Differences in gut microbiome in hospitalized immunocompetent vs. Immunocompromised children, including those with sickle cell disease. *Frontiers in Pediatrics*, *8*. https://doi.org/10.3389/fped.2020.583446