ORIGINAL ARTICLE

EFFECTS OF SUPPLEMENTING THE AMINO ACID L-CITRULLINE ON EXPERIMENTAL INFECTION WITH *Leishmania infantum* (Syn. *L. chagasi*)

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Highlights: (1). Leishmaniasis is a hypercatabolic disease. (2). L-Citrulline supplementation before infection prevented weight loss. (3). L-Citrulline supplementation during infection promoted weight gain (4). L-Citrulline supplementation may be beneficial in hypercatabolic diseases.

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ABSTRACT

Background: *Leishmania infantum* is the etiologic agent of visceral leishmaniasis, a disease that affects millions of people around the world. This study explores the therapeutic potential of supplementing the amino acid L-Citrulline in modulating the immune response and attenuating the progression of this disease in murine models**. Methods:** The study animals (isogenic BALB/c mice) were divided into two groups: Group A - supplementation started 7 days before infection; Group B - supplementation started on the first day of infection. Supplementation in both groups took place over 7 uninterrupted days with a dosage of 0.03g of the amino acid dissolved in 0.4mL of saline solution. Experimental infection occurred with the intraperitoneal inoculation of 1x106 L. infantum promastigotes. The mice's body weight was measured by the same evaluator every 7 days, from the start of the experiment until euthanasia (8th day of infection). The other parameters were assessed after the animals were euthanized. The values were tabulated and statistically analyzed. **Results:** L-Citrulline supplementation resulted in a higher percentage of body weight gain in both infected and uninfected animals during the periods analyzed. In the group treated synchronously with the infection, the infected animals showed significant weight gain when compared to those given saline solution. **Conclusion:** L-Citrulline supplementation may be a promising nutritional strategy during the treatment of L. infantum infection, so it is interesting to evaluate the effects of using this amino acid in humans and in other hypercatabolic diseases.

Keywords: Visceral leishmaniasis. Nutraceuticals. Anthropometry.

INTRODUCTION

Visceral leishmaniasis (VL) is a chronic infectious disease caused by protozoa of the genus *Leishmania* (Kinetoplastida: Trypanosomatidae)[1]. In Brazil, it is caused by the species *Leishmania infantum*, the transmission of which occurs mainly through the bite of female phlebotomines of the species *Lutzomyia longipalpis* (Diptera: Psychodidae)[2-4].

In Latin America, the disease has been described in at least 12 countries, with 90% of reported cases concentrated in Brazil, especially in the Northeast. However, visceral leishmaniasis is currently spreading throughout most of Brazil, especially in municipalities with increasing urbanization and high poverty levels[5,6]. Notifications have ceased to be centered in the Northeast region and have started to be recorded more frequently in the North, Midwest and Southeast regions of Brazil[5]. It is therefore a parasitic zoonosis that is on the rise and deserves to be highlighted for its high dissemination, with a high lethality rate, especially when associated with infections and malnutrition[7].

Studies have shown that infection with *L. infantum* (Syn. *L. chagasi*) infection has caused the loss of body stores of proteins, calories, vitamins and minerals, and therefore requires a double intervention in malnutrition and infection, as nutritional deficiencies can adversely affect immune mechanisms, depressing humoral and cellular immune function, reducing fractions of the complement system and the number, proliferation and function of circulating T lymphocytes, as well as repressing cytokine production, altering antigen recognition[8,9].

In 2022, the World Health Organization (WHO) launched the first global report on infection prevention and control, presenting the immune system as a mediator of this interaction[10]. Therefore, the lack of adequate nutritional intervention for patients with VL, with the aim of controlling weight loss and improving the immune system, can worsen the clinical picture and reduce the response to pharmacological treatment[11].

During infection by *L. infantum*, the liver undergoes various pathophysiological changes, such as increased volume, congestion and steatosis[12], and because it is an organ responsible for numerous biochemical pathways in the production, modification and utilization of nutrients and other metabolically active substances, chronic liver disease results in a major nutritional impact, regardless of its etiology[12,13]. In addition, although reduced dietary intake is considered the main factor in Protein Energy Malnutrition (PED) in liver disease, there is also a contribution from maldigestion and malabsorption[13].

Bearing in mind that the liver's functions are compromised during infection by *L. infantum*[8], and that the use of an amino acid that does not pass through the liver may be able to efficiently supply adequate amounts of nitrogen to peripheral tissues, including muscles, and thus increase protein synthesis in patients with VL, supplementation with the amino acid L-Citrulline14, which meets these criteria, may therefore be a good alternative to prevent ESD during infection.

With this in mind, the aim of this study was to evaluate the effects of supplementing the

amino acid L-Citrulline on the body biometry of BALB/c mice infected with *L. infantum* in vivo.

METHODOLOGY

Ethical aspects of animal experimentation

The trial was approved by the Ethics Committee for the Use of Animals (CEUA) of the Federal University of Piauí (UFPI), under protocol 544/2019. All procedures were carried out in accordance with the ethical requirements of the National Council for the Control of Animal Experimentation (CONCEA) and the national legislation for animal vivisection in force (Law No. 11.794, of 8/10/08, Law No. 9.605, of 12/02/98 and Normative Resolution No. 38, of 17/04/18).

Use of murine models

In order to achieve the objectives, 40 male BALB/c isogenic mice of the species *Mus musculus*, approximately 10 weeks old, were randomly selected and housed in the Leishmania Infection Room in the Sector I Animal Facility, where they were housed in plastic boxes with screens to protect against mosquitoes, and kept in a temperature-controlled environment (24ºC), with a 12-hour light-dark cycle. They were given filtered water and standard commercial feed at will. It is worth noting that the nutritional indices required for rodent feed at the UFPI Central Animal Facility are: maximum humidity of 13%, minimum crude protein of 20%, maximum ether extract of 5%, maximum crude fiber of 5% and minimum energy of 3.88 kcal/g.

Supplementation and experimental infection

The mice in the experiment were randomly divided into two groups (A and B), which were grouped according to the period in which they began supplementing with the amino acid L-Citrulline. In Group A, the amino acid supplementation started 7 days before the experimental infection (Pre-treatment) and in Group B, the L-Citrulline supplementation took place between days 1 and 7 of infection (Synchronous Treatment). It is worth noting that the experimental protocol took place over seven uninterrupted days, i.e. while the intervention animals received the amino acid for seven days without a break (treatment), those in the control subgroup (no intervention/no supplementation) received saline solution for the same period and under the same conditions.

Each group (A and B) had 20 animals, which were equally subdivided (n=10) into infected and healthy (non-infected) animals, which were distributed into subgroups "Treatment" - Intervention with L-Citrulline/positive control and "Control" - No amino acid supplementation/negative control; resulting in four subgroups for the previous treatment and four for the synchronous treatment; forming experimental subunits with a total number of 5 animals in each, numbered from I to IV, accompanied by the letter of their respective group, A or B. I - Infection and L-Citrulline; II - Infection and saline solution; III - Non-infection and L-Citrulline and IV - Non-infection and saline solution (Chart 1).

Chart 1. Division of experimental groups according to the period of initiation of supplementation.

GROUPS	**SUBGROUPS**		
		Treatment	**Control**
Previous prior (Group A) (n=20)	Infected n=10	**IA -** Infection and L-Citrulline (n=5)	**IIA** - Infection and saline solution (n=5)
	Healthy n=10	**IVA** - Non-infection and L-Citrulline (n=5)	**IIIA** - Non-infection and saline solution (n=5)
Synchronous synchronous (Group B) (n=20)	Infected n=10	**IB -** Infection and L-Citrulline (n=5)	**IIB -** Infection and saline solution (n=5)
	Healthy n=10	**IVB -** Non-infection and L-Citrulline (n=5)	**IIIB -** No Infection and saline solution (n=5)

In the subgroup of infected animals, 5 animals were supplemented (positive control) and 5 animals received only oral saline solution (negative control); in the subgroup of healthy animals (non-infected), 5 animals received amino acid supplementation diluted in saline solution and 5 received only saline solution.

The L-Citrulline supplementation protocol was based on the amount (g) of amino acid used by Batista et al.15 Thus, the animals in the intervention group received 0.03g of the amino acid dissolved in 0.4mL of saline solution to facilitate oral administration (via gavage), and the negative control group, in turn, received only 0.4mL of saline solution to simulate the same stress conditions of amino acid administration as the positive control

group.

The day of the experimental infection was considered to be day 0 (zero) of infection and took place on a Monday. Amino acid supplementation was started on Tuesday (day 1 of infection) and ended on day 7 of infection (the following Monday). The animals were euthanized on the 8th day of infection (the following Tuesday).

Group B was only handled daily during the 7 days prior to infection, so after infection they did not receive any type of treatment until euthanasia (8th day of infection). Group A, on the other hand, received no treatment in the week leading up to infection and was only handled daily between days 1 and 7 of infection, during which time they received either the amino acid (positive control/treatment) or the saline solution (negative control/no intervention) for 7 days without interruption.

For the experimental infection, purified promastigote strains of *L. infantum* (MHOM/5745) obtained in partnership with the Antileishmania Activity Laboratory of the Federal University of Piauí were used. The strains were grown in Schneider's medium (Sigma, USA), supplemented with 10% fetal bovine serum (Sigma, USA) and penicillin-streptomycin 10,000 IU/10mg (Sigma, USA) and kept in a biochemical oxygen demand oven at 26ºC. The mice in the infection group received, intraperitoneally, an infecting dose of 1x106 metacyclic promastigote forms in stationary growth phase suspended in 100µL of phosphate-buffered saline solution, and the animals in the negative control infection group, i.e. uninfected (healthy), received only saline solution to simulate the same conditions.

Monitoring body biometrics and clinical assessment

The animals' body weight was monitored at 3 different times, always at the same time, by the same assessor and scale - 7 days before infection, on the day of infection and on the 8th day of infection, when they were euthanized. They were weighed individually on a digital scale accurate to two decimal places after the gram (centigram). Each measurement was carried out in triplicate and the average of the three weighings was taken as the animal's body mass. In the end, the average weight of the last two weighings of each group (day of infection and day of euthanasia) was taken into account for analysis and comparison of results.

On the day of euthanasia, the following clinical parameters were observed and tabulated for the animals in all groups: color of the mucous membranes (eyes, mouth and nose); size of the spleen and liver; hair characteristics; and presence of ascites (enlargement of the abdominal

region due to fluid accumulation). After confirming the absence of vital parameters, the animals were dissected through a wide median abdominal incision in the ventral midline to remove the liver and spleen, which were then weighed on an analytical balance, a laboratory instrument designed to measure the mass of small samples with a high degree of accuracy and precision.

Statistical analysis

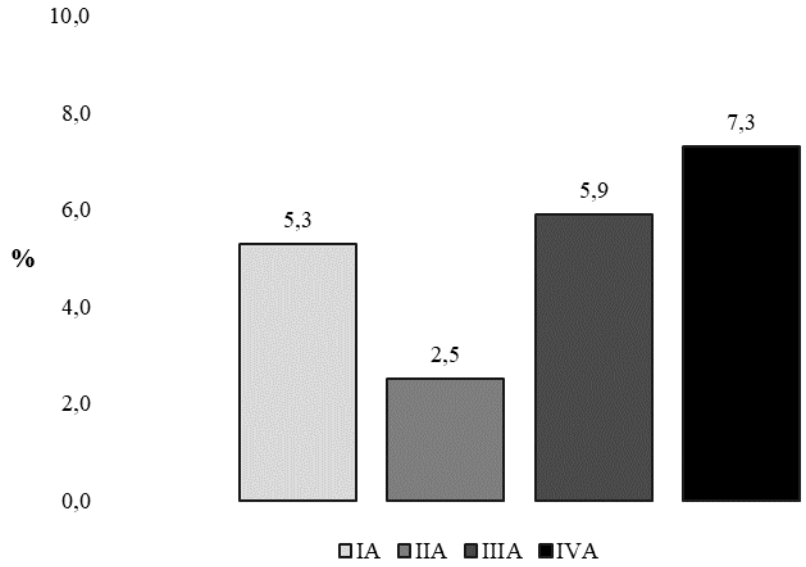
The data was tabulated in a Microsoft Office Excel® spreadsheet and analyzed using Stata® version 14 (StataCorp LP, College Station, USA). The mean, median and interquartile range were calculated. The Shapiro-Wilk test was used to verify the normality of the data (sample number) and the Mann-Whitney U test was used to analyze the difference between two variables. A significance level of less than or equal to 5% ($P \leq 0.05$) was adopted. In addition, the percentage change in the animals' weight was calculated using the following formula: % weight change = ([Current weight - initial weight]/initial weight *100).

RESULTS

The clinical assessment of the mice showed that they were normal in terms of the parameters evaluated: pink (normocolored) mucosa (eyes, mouth and nose), absence of alopecia, and no traces of hepatomegaly, splenomegaly or ascites. Comparing the median weights (g), heights, widths and depths (cm) of the liver and spleen of the animals in groups A and B, it was found that neither the infection nor the supplementation caused any significant changes between the measurements taken in the experimental and control animals. This confirms the findings of the clinical evaluation, in which the mice showed no change in the size of these organs.

All the animals that received prior treatment (group A) showed weight gain in the week after infection (Figure 1).

Figure 1. Percentage of average weight gain in group A mice after one week of infection.



Source: Research data. Caption: IA - Infection and L-Citrulline from day 1 to 7 of infection; IIA - Infection and saline solution from day 1 to 7 of infection; IIIA - Healthy and with saline solution for 7 days; IVA - Healthy and with L-Citrulline for 7 days.

It can be seen that the mice that received L-Citrulline supplementation (IA and IVA) had a higher percentage of average weight gain than their respective control group (IIA and IIIA). However, this difference was not statistically significant (Table 1).

Table 1. Comparison of the percentage change in weight gain of the animals in group (A) after one week of infection.

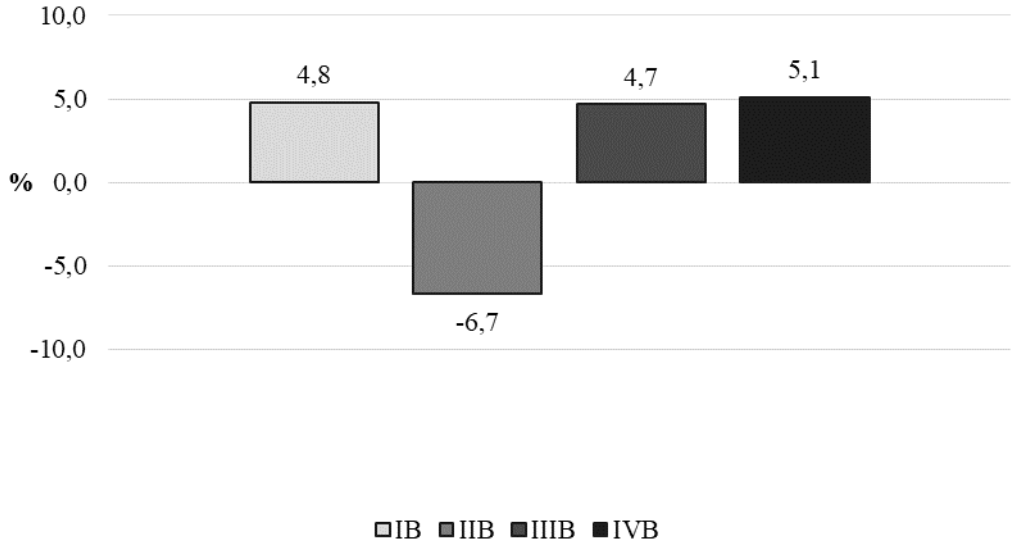
Subgroups	Variation in percentage weight gain (%)		
	Median	IQR*	P-valor
IA - Infection and L-Citrulline	5.0	3.3	0.17
IIA - Infection and saline solution	2.5	2.4	
IIIA - Saline solution	4.5	5.5	0.19
IVA - L-Citrulline	5.5	11.7	

Source: Research data. * Interval between quartiles.

In group B, corresponding to the animals that received treatment during the week of infection, the mice infected and supplemented with L-Citrulline had an increase in the percentage change in weight gain, while the control group, which only received saline, showed

a reduction of 6.7% (Figure 2).

Figure 2 - Percentage of average weight gain in group B mice after one week of infection**.**



Source: Research data. Legend: IB - Infection and L-Citrulline from day 1 to 7 of infection; IIB - Infection and saline solution from day 1 to 7 of infection; IIIB - Healthy and with saline solution for 7 days; IVB - Healthy and with L-Citrulline for 7 days.

When comparing the percentage change in the median weight of both subgroups (IB and IIB), there was a significant difference between the weight of infected animals with and without supplementation (p=0.028) (Table 2).

Table 2. Comparison of the percentage change in weight gain of group B animals after one week of infection.

Subgroups	**Variation in percentage weight gain (%)**		
	Median	**IQR**	**P-valor**
IB - Infection and L-Citrulline	7,1	9,5	0,028#
IIB - Infection and saline solution	- 6,3	- 2,2	
IIIB - Saline solution	4,5	5,5	0,190
IVB - L-Citrulline	5,5	11,7	

Source: Research data. * Interval between quartiles. #Significant difference.

DISCUSSION

L-Citrulline supplementation resulted in a higher rate of weight gain in all the groups analyzed. The study by Osowska et al. found similar results regarding the anabolic function of L-Citrulline, after investigating the effect of this amino acid on nitrogen homeostasis in aging in a model of malnourished and aged rats[16].

The results on weight gain shown by L-Citrulline supplementation may be related to the role of amino acids in the direct activation of mTOR (mammalian target of rapamycin), a protein with a central role in cell growth, proliferation and maintenance[17]. Goron and colleagues observed that L-Citrulline activated the phosphorylation of mTORC1 (mTOR Complex 1) in cultured myotubes. When activated, mTORC1 promotes anabolic processes, such as protein, nucleotide and lipid synthesis, and inhibits catabolic processes[18].

The absence of clinical manifestations in the animals in this study can be explained by the short period of time during the infection process. However, when comparing the group of infected and uninfected mice, it was found that *L. infantum* infection correlates with nutritional status even in the initial period, as the percentage of weight gain was always higher in the uninfected animals.

During the week of infection, the animals in the group that had received previous treatment were spared the discomfort and possible stress caused by forced administration (gavage), either with L-citrulline or saline solution. However, the animals in group B were stressed by the infection and the manipulation during the experimental protocol. These events may justify the results obtained in this study, since the animals in group A, which received only saline solution a week before infection, showed a weight gain, albeit small, while those in group B, under the same treatment, had a significant weight loss during infection.

Stress can affect the immune response, making the body more vulnerable in terms of its defense and thus more susceptible to infections caused by microorganisms, since natural resistance depends on the ability of cells to migrate to the site of infection, and this mechanism can be suppressed by stress[19].

In this sense, the weight loss of the infected animals that did not receive amino acid supplementation (subgroup IIB) can be explained both by the probable lack of appetite and the intense inflammatory process after the parasite entered the body, and by the possible influence of the experimental manipulation on the stress and reduction of the immune system of the animals infected by *L. infantum*, with consequent intensification of the infection. The infection,

in turn, culminates in disturbances in the metabolism of energy, proteins, minerals and even vitamins. The synthesis and utilization of these nutrients occur simultaneously. The former is represented by anabolism and the latter by catabolism. In states of inflammation, however, this process is not balanced, as there is a shift in favor of catabolism. The result is weight loss, due to the consumption of energy and protein reserves[20].

In this context, it is worth mentioning that L-Citrulline may have contributed to maintaining the body weight of the animals that used it in conjunction with the infection, as it is capable of converting into arginine, a conditionally essential amino acid which, as it serves as a substrate for immune cells, becomes extremely important during inflammation[21]. Therefore, by maintaining adequate blood levels of arginine, L-Citrulline stops the mobilization of body proteins, thus avoiding the negative energy balance and, consequently, the weight loss observed in subgroup IIB[21,22].

Thus, the data suggest that exogenous L-Citrulline seems to control protein catabolism and thus prevent weight loss in the groups that received amino acid supplementation before and during the first week of *L. infantum* infection.

CONCLUSION

L-Citrulline supplementation resulted in a higher percentage of body weight gain in animals infected or not with *L. infantum* (Syn. *L. chagasi*). In addition, it prevented the weight loss shown by the group of infected animals that did not receive the amino acid during the week of infection (negative control). Thus, the results suggest that the alternative use of nutraceuticals, such as L-Citrulline, may have the potential to reduce weight loss, and consequently improve the response to infection and treatment of leishmaniasis. It is therefore interesting to evaluate the effects of using this amino acid in humans and in other hypercatabolic diseases

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