



A Herpesvirus Relapse, After a L-arginine Overload as a Possible Trigger, and the Therapeutic Use of Its Antagonist-Competitor L-lysine: Brief Review and Case Report



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Received Date: 24 Jun 2025

Accepted Date: 01 Jul 2025

Published Date: 07 Jul 2025

Citation:

Pedrazini MC, dos Santos VAB, Pedrazini de Castilho TC, Groppo FC. A Herpesvirus Relapse, After a L-arginine Overload as a Possible Trigger, and the Therapeutic Use of Its Antagonist-Competitor L-lysine: Brief Review and Case Report. *WebLog J Amino Acids*. wjaa.2025.g0701. <https://doi.org/10.5281/zenodo.15881515>

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Abstract

Introduction: Arginine may be associated with the latent herpesvirus reactivation and L-lysine has been shown to inhibit certain viral replication phases by antagonizing arginine.

Case Presentation: Man with latent HHV-1 experienced work-related stress but only after an arginine overload, an initial recurrent labial herpes was observed. A loading dose of L-lysine was prescribed that day, followed by a maintenance dose for 30 days. Arginine-rich foods and supplements are avoided. By the sixth day, only redness, indicating the final healing stage.

Conclusion: In the presence of stress, it is advisable to avoid arginine consumption, as this may expose the individual to multiple triggers, increasing the likelihood of relapse. In this case, the lysine administration, along with a reduction in arginine intake, proved effective in controlling the episode. Further epidemiological and larger-scale studies are needed to confirm the relationship between latent virus reactivation and arginine overload.

Keywords: L-Arginine; L-Lysine; Herpesvirus; Cold Sores; Viral Diseases

High Lights – Point by Point

- The herpesvirus, for its replication, depends on important amino acids such as arginine;
- Arginine is possible associated with the reactivation of latent herpesvirus;
- It is also important to consider that certain foods contain significant amounts of Arg, mainly peanuts;
- Lysine has been shown to inhibit certain phases of viral replication by antagonizing arginine;
- Lys administration, along with a reduction in Arg intake, proved effective in viral control.

Abbreviations

HHV-1: Human Herpes Virus – 1; Lys: L-lysine, lysine; Arg: L-arginine, arginine

Introduction

Publications have highlighted the L-lysine use, (Lys)(K)a (S)-2,6,-diaminohexanoic acid, a polar basic amino acid (C₆H₁₄N₂O₂), in controlling herpes virus keratitis [1] warning about controlling L-arginine (Arg) consumption and its depletion. Arg is an essential amino acid for certain viruses and should be avoided in diet (Arg-rich foods and nutritional supplements) during viral illnesses. Its intake control as an antiviral measure has been studied over the years and during the COVID-19 pandemic, new studies have emerged with groundbreaking findings. Arg depletion via

the antagonistic amino acid Lys or recombinant arginases should be considered sparingly, as Arg plays a vital role in metabolic functions and should not be suppressed for long periods [2].

This report reinforces Tankersley's 1964 discussion, where he demonstrated that the addition of Arg to the culture medium promoted viral expression. Infected cells deprived of Arg do not facilitate viral replication; however, once this amino acid is reintroduced, immediate and extensive infection can occur [3].

It is also important to consider that certain foods contain significant amounts of Arg [2], as well as others have a high concentration of citrulline in its free form (watermelon fruit - *Citrullus vulgaris*), which contains approximately 1 g citrulline per kilogram. Citrulline can be converted into Arg via the renal pathway [4] therefore, it is also advisable to avoid citrulline-rich foods in viral conditions.

The aims of this report to present a herpes labialis case that occurred immediately following an Arg overload in the diet with the rapid control of the lesion's progression via the immediate administration of Lys together with the control of Arg intake through food. A brief review and discussion complement the clinical case.

Case Presentation

The study was conducted in accordance with the guidance from the Committee on Publication Ethics (COPE) and as outlined in the Declaration of Helsinki revised in 2013. It is approved by the Ethical Committee of São Leopoldo Mandic Institute and Research Center (Protocol # 12/0522). Informed consent was obtained from the patient for this case report publication, utilizing anonymized photographs.

In 2024, a 63-year-old man, normosystemic, with latent HHV-1 experienced significant work-related stress. During a vacation trip from August 29th, 30th and 31st, he consumed beer, chestnuts, and walnuts before lunch and dinner (around 1 cup = 150g – twice a day), daily (Figure 1A, 1B). On Monday morning, September 2nd, during a dental check-up, the dentist observed two small blisters in lower lip, near the right commissure and inquired if the patient was experiencing any discomfort. This was an initial lesion of recurrent labial herpes. The patient denied any signs or symptoms and was advised to take Lys, 3g loading dose, that day followed by a maintenance dose, 500

mg/day/30 days, always on an empty stomach with 200 ml of water. Additionally, it was recommended that he avoid foods high in Arg, such as protein-rich items.

On the second day, two additional blisters appeared however, the patient reported no pain or discomfort. The lesion was mild, and by the third day, it had progressed to the crusting stage, which persisted until the fifth day (Figure 1C). By the sixth day at night, there was no more crusting, only redness, indicating the final healing stage. Notably, the patient had experienced a similar lesion on the upper lip in 2007, which was larger than the current one in the same period, five days (Figure 1D) and still in the bullous phase. Reviewing the clinical record, the patient started Lys, 500mg/day, at the end of the injury, on the seventh day (Table 1).

The patient also reported that certain triggers like very cold temperatures or sun exposure without lip protection, associated or not with stress, often lead to relapses in various areas of the lip, including the upper right lip, lower right lip, or labial tubercle region near the cupid's bow. He observed that with each relapse, when he used Lys at the lesion onset, the outbreaks became progressively smaller, less severe, and resolved more quickly. This was the first time, according to the patient, that a lesion appeared following a significant Arg intake. Although he had not previously linked his outbreaks to Arg consumption, upon discussing the triggers, he immediately associated the excessive intake of chestnuts and walnuts, as potential contributing factor.

Discussion

Arg is obtained from three sources: endogenous *de novo* production through normal cellular protein breakdown (recycling), tissue protein degradation which provides an alternative fuel source during fasting or uncontrolled diabetes mellitus and, dietary proteins [4]. It is a natural human diet component, found in all proteins of both animal and plant origin, and is classified as a proteinogenic amino acid [5]. Average Arg intake from Western-style diet is approximately 4–5 g/day, with normal plasma levels ranging from 100 to 200 μM [4].

Cashew nuts, peanuts and almonds, consumed by this patient, are foods rich in Arg (4 g/cup of arginine – twice a day) with a content 2.6 to 4.7 times greater than that of its antagonist Lys, an antiviral agent [6]. This could mean consuming 8 grams more arginine than is contained in a normal diet.

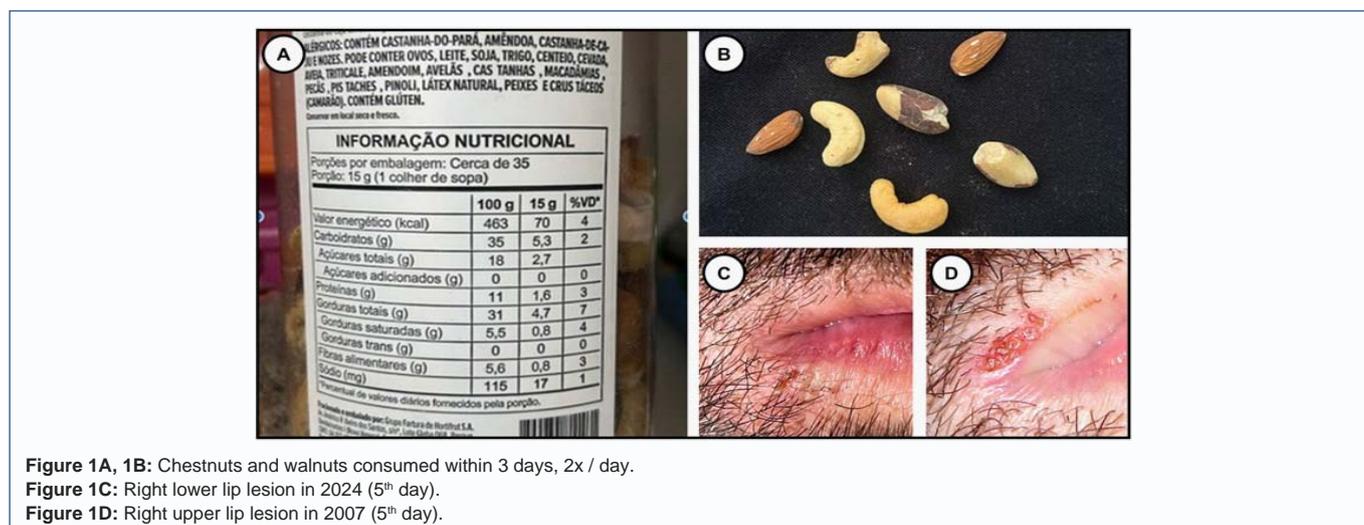


Figure 1A, 1B: Chestnuts and walnuts consumed within 3 days, 2x / day.

Figure 1C: Right lower lip lesion in 2024 (5th day).

Figure 1D: Right upper lip lesion in 2007 (5th day).

Source: All photos were taken by the main author.

Table 1: Timeline of the oral herpes simplex.

2007	Herpes Simplex lesion on the upper lip	Stinging, burning, pain, blistering phase, crust (larger)	L-Lysine started in the final phase of the crust, on the seventh day (500 mg/day, on an empty stomach and with a glass of water, until completing 30 days.)	On the ninth day he was asymptomatic and in the final stage of healing, without a scab
2024	August 29 th , 30 th , 31 st Consumed beer, chestnuts, and walnuts before lunch and dinner, daily	No signs or symptoms of herpes recurrence		
2024	September 2 nd - first day During a dental check-up and oral prophylaxis, the dentist observed two small blisters near the right commissure of the lower lip	Patient denied the presence of symptoms	A loading dose of 3 grams of Lys that day, followed by a maintenance dose of 500 mg until 30 days are completed, always on an empty stomach with 200 ml of water. Additionally, it was recommended that he avoid foods high in Arg, such as protein-rich items	Minor and much milder injury compared to the one in 2007
2024	September 3 rd - second day Two additional blisters appeared	However, the patient reported no pain or discomfort	L-lysine 500 mg/day an empty stomach with 200 ml of water. Additionally, it was recommended that he avoid foods high in Arg, such as protein-rich items	Minor and much milder injury compared to the one in 2007
2024	September 4 th - third day The lesion was mild and had progressed to the crusting stage.	The patient reported no pain or discomfort	L-lysine 500 mg/day an empty stomach with 200 ml of water. Additionally, it was recommended that he avoid foods high in Arg, such as protein-rich items	Minor and much milder injury compared to the one in 2007
2024	September 5 th - fourth day Final crusting stage	The patient reported no pain or discomfort	L-lysine 500 mg/day an empty stomach with 200 ml of water. Additionally, it was recommended that he avoid foods high in Arg, such as protein-rich items	Minor and much milder injury compared to the one in 2007
2024	September 6 th - fifth day Final stage, little scab	The patient reported no pain or discomfort	L-lysine 500 mg/day an empty stomach with 200 ml of water. Additionally, it was recommended that he avoid foods high in Arg, such as protein-rich items	On the sixth day he was asymptomatic and in the final stage of healing, without a scab

Source: Provided by authors.

Elevated serum Arg levels may facilitate the development of cold sores (HHV-1), an arginine-dependent virus. On the other hand, viral expression is inhibited by high intracellular Lys levels. When serum levels are analyzed, viral activity is suppressed when Lys concentrations exceed 165 nmol/ml; however, when these levels fall below this limit, viral reactivations occur. The absolute concentration of Arg may not be a significant factor when serum Lys levels are adequate, but the Lys/Arg ratio, considered crucial, did not show clear patterns [7].

Lys and Arg are structurally related molecules that may compete for the same transporters during intestinal absorption and for transport across cell membranes [8]. Due to the competitive antagonism between Lys and Arg [6], the greater intake of Arg by the patient may have led to a decrease in serum Lys levels, since in some cases a cellular inability to absorb Lys was observed, which is the greatest challenge to the efficacy of this amino acid [7]. However, by restoring Lys levels through a 3g loading dose followed by maintenance with Lys, 500 mg/day, viral replication can be interrupted [1,2], which explains the control of the evolution of the lesion in this clinical case as well. Additionally, Lys promotes an increase in renal arginase, which catabolizes Arg [6].

The reactivation of herpesviruses can be triggered by various factors, including specific hormonal conditions, stress, cold weather, solar radiation, and situations involving immune system depression or activation [9] but latent herpesviruses may remain dormant due to the unavailability of Arg. Viral synthesis is impaired and the formation of complete viral particles is inhibited. When Arg is sufficiently available, the likelihood of rapid and widespread reinfection increases [3]. This is the hypothesis in this clinical case because even though the patient had been facing a reactivation trigger (stress) for several months, the virus was only reactivated by the arginine load.

Therefore, controlling the imbalance between Lys and Arg

is crucial. Increasing the supply of Lys, either through diet or supplements, may be beneficial in the context of certain infections [6].

Theoretically, ingestion of Lys 3g loading dose during the onset of a viral outbreak is safe. Approximately 4–5 g/day of Lys from dietary sources is ingested per day and a loading dose of 3g would not exceed the limit of 7500/8000 mg/day. Above these doses, intestinal discomfort has been demonstrated according to the study conducted by Hayamizu and colleagues [10].

It is crucial to provide an effective antiviral treatment during each reactivation event, as this can reduce the number of viral particles present in the neural pathways. Recurrent HHV-1 infections have been linked to accelerated neuronal aging, which is associated with an increased risk of neurodegeneration and Alzheimer's disease [11].

Lys protocol should be started during prodromal stage to interfere with the viral replication cycle, which peaks within the first 24 to 48 hours [1,2]. This explains the severity of the 2007 lesion. The patient started Lys 500 mg at the crust stage, the final cycle. Since then, upon the first appearance of prodromal signs, the patient began Lys 3g loading dose and then maintained 500 mg/day for a few more days, always on an empty stomach, resulting in milder lesions, often regressing without progressing to the bullous phase.

Lys has been used as an antiviral agent, mainly by depleting arginine, demonstrating efficacy in reducing viral infections incidence, lesions number and severity, and the healing time. This is particularly evident when treatment is initiated during the early days of manifestation, coinciding with the viral multiplication phase [6].

It is important to inform that arginine has a significant metabolic function and should not be depleted for long periods of time, resulting in nutritional losses and consequently interfering with cellular metabolism. Its depletion as an antiviral action should only

be indicated in active viral infections or in the presence of other triggers in latent virus carriers [2].

Conclusion

Additional epidemiological studies are needed to confirm the relationship between latent viral reactivation and Arg overload. Administration of Lys associated with reduced Arg intake has been shown to be effective in controlling the episode. In the presence of a potential trigger, it is advisable to avoid high Arg intake, reducing the risk of viral reactivation by exposure to multiple triggers.

Authors' Contributions

M.C.P. and F.C.G. equally contributed to the conception and design of the research; M.C.P. contributed to the acquisition and analysis of the data and drafted the manuscript; V.A.B.S. contributed to figure formatting and editing; T.C.P.C. contributed to editing and proofreading of the manuscript in English. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Declarations

Ethics Approval: The study was conducted in accordance with the guidance from the Committee on Publication Ethics (COPE) and as outlined in the Declaration of Helsinki revised in 2013. It is approved by the Ethical Committee of São Leopoldo Mandic Institute and Research Center (Protocol # 12/0522).

Consent to Participate: Informed consent was obtained from the patient for this case report publication, utilizing anonymized photographs.

Consent for Publication: We have the consent of the patient.

Availability of Data and Material: The health record data used is restricted to protect patient privacy. When appropriate, certain data from health records are included verbatim in the article. Data used in the discussion were sourced from peer-reviewed journals and previously published case reports. Appropriate citations and references are included in the article.

Competing Interests: The authors declare no competing interests.

Funding: This study did not receive funding.

Code Availability: Not applicable.

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