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MARIA CRISTINA PEDRAZINI DE CASTILHO

O EFEITO ANTIVIRAL DO AMINOÁCIDO L – LISINA

THE ANTIVIRAL EFFECT OF THE L-LYSINE AMINO ACID

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MARIA CRISTINA PEDRAZINI DE CASTILHO

O EFEITO ANTIVIRAL DO AMINOÁCIDO L – LISINA

THE ANTIVIRAL EFFECT OF THE L-LYSINE AMINO ACID

Tese apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Doutora em Odontologia, na Área de Farmacologia, Anestesiologia e Terapêutica.

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Orientador: Prof. Dr. Francisco Carlos Groppo

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“ SE NÃO PUDER VOAR, CORRA.
SE NÃO PUDER CORRER, ANDE.
SE NÃO PUDER ANDAR, RASTEJE MAS
CONTINUE EM FRENTE DE QUALQUER JEITO.”

Martin Luther King

“DIVIDIR O CONHECIMENTO É
UMA FORMA DE SE TORNAR IMORTAL”

Dalai Lama

RESUMO

A COVID-19 representa um desafio tamanho é o espectro de sinais e sintomas observados nos pacientes acometidos. Tanto a doença como as vacinas anti SARS-CoV-2 podem reativar os vírus da família *Herpesviridae,* cuja principal característica é a latência vitalícia. Quando reativados, por diversos fatores, vão causar desconforto, dor, aumento de morbidade em imunossuprimidos ou naqueles acometidos de outras doenças, aumento dos riscos de encefalites, ceratites e demência por Alzheimer. Diante disso, evitar as reativações ou imediatamente tratá-las, pode auxiliar na prevenção destas sequelas. O conhecimento das características do vírus, do hospedeiro e da relação entre eles, pode favorecer o desenvolvimento de terapias antivirais. Fatores relacionados à alimentação podem favorecer a multiplicação viral, aumentando a gravidade de uma doença e a depleção e suplementação de aminoácidos contidos na alimentação podem levar às novas alternativas profiláticas e/ou terapêuticas antivirais. Objetivo deste trabalho foi estudar, por meio de uma revisão de literatura, o efeito antiviral da L-lisina e relatar dois casos clínicos de pitiríase rósea tratados com este aminoácido. A L-Lisina interferiu positivamente no controle desta manifestação por herpesvírus 6/7, da mesma forma que já se mostrava promissora no controle da herpes simples. Sua ação antiviral está relacionada com seu antagonismo por competição com a L-arginina, essencial à multiplicação e infectividade viral, além de seu potencial de promover um aumento da arginase humana, fazendo a depleção da arginina e controlando a doença viral. Embora existam evidências sobre a importância desses aminoácidos no controle de alguns vírus da família *Herpesviridae,* mais estudos são necessários sobre esse controle em outros vírus de interesse.

Palavras-chave: L-lisina. L-arginina. Aminoácidos. Vírus. Herpesvírus. Pitiríase rósea. Vacinas. SARS-CoV-2. COVID-19.

ABSTRACT

COVID-19 represents a challenge such as the spectrum of signs and symptoms observed in affected patients. Both the disease and vaccines against SARS-CoV-2 can reactivate viruses from the Herpesviridae family, whose main characteristic is lifelong latency. When reactivated, due to several factors, they will cause discomfort, pain, increase in morbidity in immunosuppressed patients or in those affected by other diseases, and increase the risk of encephalitis, keratitis and Alzheimer's dementia. Therefore, avoiding reactivations or immediately treating them, can help prevent these sequelae. Knowledge of the characteristics of the virus, the host and the relationship between them can favor the development of antiviral therapies. Factors related to diet can favor viral multiplication, increasing the severity of a disease and the depletion and supplementation of amino acids contained in food can lead to new prophylactic alternatives and/or antiviral therapies. The aim of this work was to study, through a literature review, the antiviral effect of L-lysine and to report two clinical cases of pityriasis rosea treated with this amino acid. L-Lysine positively interfered in the control of this manifestation by herpesvirus 6/7, in the same way that it already showed promise in the control of herpes simplex. Its antiviral action is related to its antagonism by competition with L-arginine, essential for viral multiplication and infectivity, in addition to its potential to promote an increase in human arginase, depleting arginine and controlling viral disease. Although there is evidence on the importance of these amino acids in the control of some viruses of the Herpesviridae family, further studies are needed on this control in other viruses of interest.

Keywords: L-lysine. L-arginine. Amino acid. Virus. Herpesvirus. Pityriasis rosea. Vaccines. SARS-CoV-2. COVID-19.

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1 INTRODUÇÃO

As infecções virais representam uma grande ameaça para a saúde humana, sendo os vírus os principais patógenos causadores da morbidade e mortalidade no mundo (Jiang et al., 2016; Adda, 2016; Vilas-Boas et al., 2017).

Estudos demonstram que cerca de 60% das infecções humanas são de origem viral, principalmente infecções respiratórias e entéricas (Neto et al., 2013) e de acordo com os dados históricos do último século, as epidemias virais foram responsáveis por um número de óbitos superior aos conflitos armados no mesmo período, a exemplo da varíola (300 milhões de mortos) e influenza (100 milhões) (Adda, 2016). Em março de 2022, com um pouco mais de 2 anos de pandemia pelo SARS-CoV-2, já se contabiliza 6.019.085 de mortes por COVID-19 (WHO, 2022).

Essas infecções sempre foram alvo de grande preocupação no sistema de saúde posto que as mudanças nos indicadores demográficos, socioeconômicos e fatores de risco, favorecem o surgimento e a transmissão de patógenos virais conhecidos ou novos (Luna e Silva, 2013).

A pandemia global causada pelo SARS-CoV-2 (COVID-19) levou a uma morbidade e mortalidade significativas e a uma interrupção econômica e do sistema de saúde sem precedentes (Khanolkar et al., 2022).

O conhecimento das características estruturais e comportamental dos vírus, ajuda na sua classificação além de aumentar o entendimento sobre a interação de suas proteínas no ciclo de multiplicação, disseminação e na própria relação vírus-hospedeiro, e nesta relação, fatores ambientais, idade, estados fisiológicos e nutricionais, podem favorecer a perpetuação desses agentes infecciosos (Stephens et al., 2009)

Entender a relação e as características dos envolvidos, vírus/hospedeiro, é necessário para o desenvolvimento de novos fármacos antivirais e para auxiliar a implementação de programas terapêuticos tanto para o controle como para a prevenção das infecções, buscando restringir a disseminação de vírus emergentes e reemergentes capazes de iniciar episódios epidêmicos (De Clercq e Li, 2016; Vilas-Boas et al., 2017; 2019) e até mesmo pandêmicos (Wollina, 2020).

Vírus, viroides, virusoides e príons são os menores agentes infecciosos, apresentam diversas formas (icosaédrico, helicoidal, retangular ou complexo), os diâmetros variam de 20 a 1200 nm e são capazes de infectar plantas, animais e bactérias além do homem (Abrahão et al.,

2018). Porém, são incapazes de completar seu ciclo de replicação fora de uma célula hospedeira, o que os caracteriza como parasitas intracelulares (Irwin et al., 2016).

Fatores biológicos promovem altas taxas de mutações com alterações em componentes estruturais virais como enzimas e proteínas, leva à resistência aos fármacos (Saxena et al., 2010) como também à esquiva do sistema imunológico, o que pode causar reinfecções (Tognarelli et al., 2019).

De acordo com seu genoma, se classificam como RNA vírus com multiplicação em citoplasma celular (coronavírus, influenza vírus e retroviridae) ou DNA vírus com multiplicação intranuclear (herpesvírus, adenovírus e hepadinaviridae). As macromoléculas (DNA ou RNA) se encontram inseridas no capsídeo que é formado de capsômeros (glicoproteínas). O conjunto (capsídeo + macromolécula) denomina-se nucleocapsídeo e alguns vírus possuem ainda o tegumento, proteínas não-estruturais importantes para a formação de outra estrutura, o envelope viral, formada pelas proteínas virais e proteínas do hospedeiro advindas de parte da membrana plasmática que é carregada durante a saída do vírus da célula. São as glicoproteínas virais do nucleocapsídeo ou do envelope, no caso de vírus envelopados, que exercem importante papel na interação com receptores da célula alvo (Ryu, 2017).

Uma alta taxa de mutação é um desafio significativo no desenvolvimento de antivirais contra RNA vírus, e essas mutações podem beneficiar o ciclo de vida viral fazendo com que ocorra uma evasão à resposta imune, aumento de transmissibilidade e patogenicidade (Melano et al., 2021). A principal diferença entre vírus DNA como herpesvírus e RNA como coronavírus e influenza vírus, está na enzima polimerase de cada tipo viral. A maioria dos DNA vírus copiam seu material genético usando uma enzima chamada DNA polimerase que irá duplicar o material genético e revisar o DNA verificando erros e, ao mesmo tempo, os corrigindo durante as cópias. Os RNA vírus usam a enzima chamada RNA polimerase que não realiza checagens e correções permitindo infinitos erros que são transmitidos aos vírus filhos, mutados (Fleischmann, 1996).

A entrada viral consiste de vários eventos sequenciais que garantam a sua fixação na célula hospedeira e a introdução de seu material genético para a continuação do ciclo de replicação (Nieto-Garai et al., 2022) e na maioria dos vírus envelopados, as etapas da entrada viral incluem ligação, endocitose ou fusão do envelope, internalização do núcleo capsídeo com posterior desencapsulamento e injeção do material genético, para em seguida, dar início as etapas de replicação onde os aminoácidos têm sido implicados como coadjuvantes (Melano et al. 2021).

Herpesviridae é uma família complexa e subestimada. Sabe-se que os vírus HHV-1 e HHV-2 são os responsáveis por causar o herpes labial e genital respectivamente. Estima-se que 3,7 bilhões de pessoas com menos de 50 anos (67%) tenham infecção por HHV-1 em todo o mundo enquanto 491 milhões de pessoas entre 15 e 49 anos, 13% da população mundial, esteja carregando o HHV-2 (WHO, 2020) porém, o HHV-1 não ataca somente a região orofacial e o HHV-2 a região genital, ambos são capazes de infectar as duas regiões (Rechenchoski et al., 2017).

Compreende uma grande família de vírus DNA, envelopados, de macromolécula de cadeia dupla e que infectam tanto animais como humanos, mas nestes, foram identificados apenas oito herpesvírus com capacidade de infectá-los (Siakallis et al., 2009). A população adulta, quase 100% dela, já está infectada com pelo menos um deles que são: vírus do herpes simples tipo 1 e 2 (HSV)(HHV-1/2), vírus varicela zoster (VZV)(HHV-3), vírus Epstein Barr (EBV)(HHV-4), citomegalovírus (CMV)(HHV-5), roseovírus (HHV-6/7) e oncovírus (HHV-8), sendo um deles o KSHV, responsável pelo sarcoma de Kaposi (Grinde, 2013).

Sua principal característica é a latência vitalícia (Gatherer et al., 2021) e após estabelecida, a reativação ocorre devido à estímulos locais ou sistêmicos como stress físico, mental, febre, exposição aos raios ultravioletas, extremo frio, dano tecidual e imunossupressão. Dependendo de inúmeros fatores, a reativação pode ser assintomática ou levar a uma lesão recorrente local ou sistêmica, acometendo também pacientes imunocompetentes, mas principalmente àqueles em unidades de terapia intensiva (UTI), o que aumentará a morbidade e mortalidade (Simonnet et al., 2021).

Durante a pandemia de COVID-19, os herpesvírus têm se manifestado em uma porcentagem muito maior quando comparada à períodos anteriores, principalmente nos acometidos pela COVID-19 e isso tem causado uma grande preocupação para a classe médica (Fernandez-Nieto et al., 2020) pois nestes pacientes, já imunocomprometidos por esta doença, a reativação dos herpesvírus resultaria em maior prejuízo levando a implicações clínicas como também prognósticas (Katz et al., 2021).

Infecções por herpesvírus como o HHV6/7 (roseovírus), responsáveis pela manifestação dermatológica primária e exantemática chamada de exantema súbito ou roséola infantil. Esses vírus também são causadores, quando reativados, de uma manifestação eritematosa, papulosa e escamosa chamada pitiríase rósea (PR) que foi relatada previamente à própria manifestação da COVID-19 (Martín et al., 2020; Eghbali e Hosseinzadeh, 2021;

Welsh et al., 2021) e em alguns casos, a manifestação clínica da PR foi relatada como único sintoma da infecção pelo SARS-CoV-2 (Martín et al., 2020), o que poderia estabelecer uma relação direta entre a infecção por herpesvírus e uma forma latente da COVID-19 (Katz et al., 2021).

Sabe-se que vários gatilhos podem desencadear a saída destes vírus de seu estado de latência (Freitas et al., 2003; Miranda et al., 2008) e fatores como a oncogene, a hipóxia e infecções virais estão também nesta lista (Nausch e Cerwenka, 2008). A infecção viral e possível posterior hipóxia, estão presentes na COVID-19 explicando o aumento nas reativações de herpesvírus (Dursun eTemiz, 2020; Ehsani et al., 2020; Fernandez-Nieto et al., 2020; Martín et al., 2020; Siddiqui e Hasnain, 2020; Welsh et al., 2021, Veraldi e Spigariolo, 2021).

Diante desta atual pandemia, os esforços não foram medidos para que se encontrasse imunizantes em tempo recorde e com a chegada deles, reações adversas como reativações desses vírus latentes, também foram observadas após seu uso (Ardalan et al., 2021; Marcantonio-Santa Cruz et al., 2021; Richardson-May et al., 2021; Fathy et al., 2022).

Em abril de 2021, com 3 meses de vacinação, já havia 672 casos de possíveis reações cutâneas relacionadas somente às vacinas chamando a atenção de que além do aumento de reações semelhantes à PR, houve vários relatos de casos de herpes simples e herpes zoster pós vacinas (Fathy et al., 2022).

Além de vacinas, é importante manter um foco na busca de novas moléculas antivirais para tratamentos clínicos. O crescente número de relatos de resistência viral aos antivirais atuais e o surgimento de novos tipos de vírus tem preocupado a comunidade científica. As abordagens atuais provaram ser insuficientes em alguns casos. Muitas alternativas são propostas hoje em dia e os peptídeos antivirais estão entre elas, mas, no entanto, mesmo que existam vários peptídeos descritos como antivirais, poucos realmente chegam à fase de ensaio clínico (Vilas-Boas et al., 2017; 2019).

Os principais fármacos utilizados no tratamento das infecções pelos vírus da família do herpesvírus são os análogos de nucleosídeos mais especificamente os análogos de guanosina cíclico como Aciclovir (ACV), Valaciclovir (VCV), Penciclovir (PCV), Famciclovir (FCV), Ganciclovir (GCV) e Valganciclovir (VGCV), além dos análogos de citosina (Cidofovir) e o análogo de pirofosfato (Foscarneto) (Rechenchoski et al., 2017; Ehrenstein, 2020) e algumas

dessas drogas são reservadas a pacientes imunocomprometidos e com herpes simples severa (Crimi et al., 2019; Bunz et al., 2020; Silva-Alvarez et al., 2021).

O aciclovir, um inibidor de DNA polimerase, é um dos antivirais mais prescritos para o tratamento das manifestações de herpesvírus (Pedrazini et al., 2018; Rodriguez-Zuniga et al., 2018; Chang et al., 2019; LoBue et al., 2019, 2020), sendo considerado padrão ouro (Stoopler et al., 2003; Santosh e Muddana, 2020) principalmente no tratamento da pitiríase rósea, reativação do roseovírus (HHV-6/7), da herpes zoster (HHV-3) e de herpes simples (HHV1/2) (Chang et al., 2019; LoBue et al., 2019; 2020; Schuierer et al., 2020; Bunz et al., 2020).

Este antiviral, assim como outros, atua nas etapas iniciais da replicação e o sucesso da terapia pode ser comprometido se a intervenção terapêutica não ocorrer durante os primeiros estágios da infecção, afim de impedir a replicação viral e a evolução dos sinais e sintomas da doença (Pedrazini et al., 2007; 2018; Chang et al., 2019).

A terapêutica iniciada já no período ativo da infecção ou sua eventual descontinuidade, constituem fatores que diminuem a eficácia do tratamento como aumenta os riscos do surgimento de cepas resistentes, o que acomete mais pacientes imunocomprometidos (2,5-25% de cepas resistentes) e em menor porcentagem os imunocompetentes (0,3-0,7%) (Birkmann e Zimmermann, 2016).

Estudos demonstraram que os vírus controlados pelo aciclovir como o HHV-1, também puderam ser controlados pelo aminoácido L-lisina sendo uma alternativa antiviral promissora. O protocolo profilático com 500 mg/dia de L-lisina ingerida em jejum com 200 ml de água, se mostrou eficaz na redução no número de reativações anuais de herpes simples. Diante de reativações, a terapia com 3 g de lisina, dose única de ataque, aplicada precocemente juntamente com uma redução do aminoácido arginina, um pró vírus, se mostrou eficaz na redução da gravidade das lesões e no tempo de cicatrização, involuindo muitas lesões ainda no período prodrômico ou no clínico inicial (Pedrazini et al., 2007, 2018).

Mesmo que o paciente não consiga iniciar nestes períodos, ainda assim, o tratamento com L-lisina pode ser benéfico em estágios mais avançados, promovendo um período de reparo mais rápido por auxiliar na produção de colágeno e elastina (Pedrazini et al., 2007), como discutido no artigo 3 (Pedrazini et al.)

Sabe-se que uma única partícula de vírus (vírion) não pode replicar ou expressar material genético (DNA, RNA) sem a disponibilidade de aminoácidos. Essas substâncias

desempenham um papel importante nas infecções relacionadas à vírus sendo necessária para a síntese proteica e regulação de vias metabólicas, incluindo a expressão gênica. A ausência de aminoácidos essenciais ao vírus como a L-arginina (Kagan, 1974; Griffith et al., 1981; Sanchez et al., 2016) pode resultar em partículas virais vazias, livres de ácidos nucleicos (Tankersley, 1964; Butorov, 2015) ou partículas desnudas, sem capsídeo, com o DNA exposto às DNases do núcleo (Becker et al., 1967). A consequência é a geração de vírus não maduros, sem ação viral.

Uma das possibilidades a ser discutida é justamente o uso da L-lisina como um antiviral indireto uma vez que este aminoácido disputa pelos mesmos transportadores do aminoácido L-arginina como também promove o aumento da produção da enzima arginase 2 nos túbulos renais degradando a arginina e consequentemente controlando a infecção (Gaby, 2006; Pedrazini et al., 2018).

O controle de arginina tem sido investigado como uma potente estratégia antiviral contra vírus da família Herpesviridae HHV-1 (Pedrazini et al., 2007; 2018), HHV-3 (LoBue et al., 2019; 2020), HHV-5 (Garnett, 1975); HHV-6/7 (Roxo et al., 2018).

Diante desta possibilidade, o objetivo deste trabalho foi estudar por meio de uma revisão de literatura, o efeito antiviral da L-Lisina e relatar dois casos clínicos de pitiríase rósea tratados com este aminoácido.

2 ARTIGOS

2.1 L-lysine therapy to control the clinical evolution of pityriasis rosea: Clinical case report and literature review

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REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

L-lysine therapy to control the clinical evolution of pityriasis rosea: Clinical case report and literature review

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Abstract

Pityriasis rosea (PR) is a dermatological disease with an erythemato-papulosquamous manifestation, distributed on the trunk and extremities affecting healthy people, especially children and young people between 10 and 35 years of age. The evolution is 6 to 8 weeks and may remain for 3 to 6 months. It regresses spontaneously and can leave changes in the skin color but reversibly. Acyclovir is indicated to minimize clinical manifestations with the suspected of viral association (HHV-6 and 7). Another group of the human herpesvirus family (HHV-1 and 2), causes herpes simplex that is controlled with the antivirals, including acyclovir, as well as the amino acid L-lysine, both showing positive and similar results in reducing the number of annual manifestations and the healing time of the lesions. The aim of this study is to report a case of PR in a child, to review the literature on the etiopathogenesis of the disease and on the effects of L-lysine as well as another amino acid in the treatment. An 11-year-old girl, phototype II, presented lesions diagnosed as PR. The cycle would be 6 to 8 weeks on average. A solution of L-lysine was prescribed for 30 days, on an empty stomach. After the fourth day of therapy, the cycle of new eruptions was interrupted, initial lesions regressed, accelerating the repair of larger lesions resulting in an improvement of the clinical condition. We concluded that the administration of L-lysine, in therapeutic doses, can be a safe alternative for the PR control.

KEYWORDS
amino acid, human herpesvirus 6-7, L-lysine, pityriasis rosea

1 | INTRODUCTION

Pityriasis rosea (PR) is a skin disease characterized by the erythemato-papulosquamous manifestation, distributed in trunk, and extremities.[1]

It begins with primary lesion, single, oval, pink, peeling in the periphery known as "mother patch" or "herald patch". It has centrifugal growth, reaching 2 to 10 cm in diameter, remaining isolated for 1 to 2 weeks, when new minor secondary lesions, 0.5 to 1.5 cm, appear in the chest, abdomen, back and proximal extremities of the limbs coexisting with the mother patch.[2]

Described in 1860 by Camille Melchior Gibert, it affects healthy people, especially children and young people between 10 and 35 years of age.[1] Currently, it has been associated with a dermal manifestation of SARS-COV-2 (COVID-19), which is an important alert to dermatologists[3]

The evolution varies from 6 to 8 weeks and may remain from 3 to 6 months. It regresses spontaneously, leaving reversible changes in skin color.[4] A survey between 2003 and 2014 with 613 patients, showed that the prevalence does not obey seasons, and may arise throughout the year.[5]

Although most cases have a classic clinical condition, several atypical variants of the disease have been recorded.[1,6] The "herald patch" may not be present not excluding the diagnosis,[2] as can it be the only manifestation.[7]

PR is generally asymptomatic and self-limiting, requiring no treatment. Self-medication should be avoided because some substances

cause irritation. In scaly conditions, severe itching or residual stains, the dermatologist should be consulted. Despite spontaneous resolution, in certain situations, drugs such as antihistamines and corticosteroids help with itching. Sunbathing is also indicated for itching as an improvement in residual white spots. The benefits of these treatments are still topics of discussion, given the lack of knowledge of the PR etiology.[2]

Several etiopathogenic factors for PR were considered as insect bites that could activate an inflammatory response triggering the typical rash of the disease.[8] Over the years, fungi, bacteria, and viruses have been suggested. The possibility of involving autoimmune processes and genetic susceptibility, as well as states of immunodepression, atopy, and pharmacological idiosyncrasies, have also been pointed out.[9] Some of the characteristics suggest that it is an infectious process, which more recent trends attribute to a virus.[5,10]

An in vitro study found viral particles, analogous to picornavirus, intranuclear and intracytoplasmic in the epidermis keratinocytes, suggesting viral agents as possible causes of PR.[11] Subsequently, other viruses were investigated, such as togavirus, arenavirus, adenovirus, influenza AB virus, parainfluenza 1-2-3, respiratory syncytial virus, cytomegalovirus, Epstein-Barr virus, parvovirus B19, without demonstrating their participation in the disease etiology.[12,13] Other studies have associated a possible infection with human herpesvirus (HHV-6 and 7) as the cause of PR.[10,14,15]

The herpes simplex (HS) viruses, HHV-1 and 2, such as the human herpesvirus HHV-8, were also investigated, with no demonstration of a possible association with PR.[16,17]

With the suspected association of PR with HHV-6 and 7 viruses, acyclovir was indicated showing positive results, easing the clinical condition.[18]

Acyclovir is also part of the treatment of HHV-1 and HHV-2 viruses' manifestation, softening the clinical picture. Another alternative for the control of HS is the therapy with the use of an essential amino acid, L-lysine, which showed reduction in the annual manifestations number as well as in the healing time of lesions caused by these viruses.[19,20]

L-lysine has been indicated for the treatment of HS (HHV-1), because it presents similar results to the antiviral acyclovir.[19,20] Since acyclovir has been indicated for the control of PR, due to its association with HHV-6 and 7,[18] the aim of this study is to report a case of PR in a child, to review the literature on the etiopathogenesis of the disease and on the effects of L-lysine as well as another amino acid in the PR treatment.

2 | CASE REPORT

A written consent form was obtained from the parents responsible for the child, aiming at reporting the case.

A 11-year-old girl, 32 kg, phototype II, was in July 2017 on beaches in the northern hemisphere (summer). In Brazil, on July 18 (winter), a reddish, erythematous lesion was noticed, with mild itching in the left thigh like an insect bite. After 7 days, the lesion was larger, approximately 2 cm and scalier in appearance. (Figure 1(A)) when the dermatologist was consulted. Other lesions were noted on the abdomen with a scaly aspect (Figure 2(A)), in addition to small lesions spread on the chest.

In May of the same year, the child had received a dose of the influenza vaccine (H1N1), without adverse reactions and during the trip she used a suspension of 6 mg/mL of fexofenadine hydrochloride, in a dose of 5 mL every 12 hours for 3 days due to several mosquito bites. In addition, she had Roseola (HHV-6) at 2-years-old and her father also had a cold sore (HHV-1).

Based on the history and the clinical condition, the diagnosis of PR was made. The cycle would be 6 to 8 weeks of continuous rashes with subsequent scaling and scarring, with whitish spots on the skin that would regress with time and sunbathing.

Sunbathing was also indicated for pruritus, before 10 AM or after 4 PM, as the use of the suspension of 6 mg/mL of fexofenadine hydrochloride in the dose of 5 mL every 12 hours if necessary. The dermatologist' instructions were followed, but more injuries appeared in the subsequent days when an oral solution of L-lysine 250 mg/5 mL was

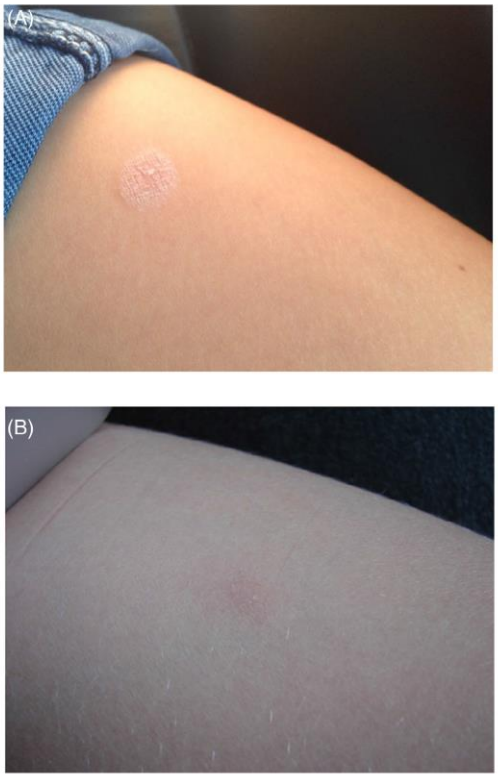

FIGURE 1 (A) Mother patch - left thigh - 8th day; (B) Mother patch - left thigh - 24th day

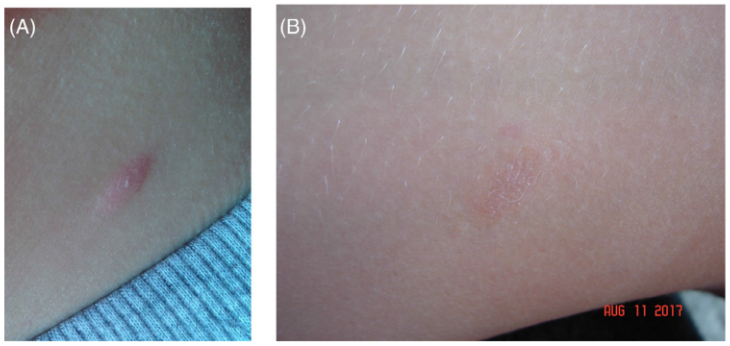

FIGURE 2 (A) Secondary injury - abdomen - 8th day; (B) Secondary injury - abdomen - 25th day

prescribed. The therapy was initiated with 2 weeks of evolution of the PR, being administered 5 mL/day in absolute fasting, waiting 20 minutes for breakfast and control of the intake of L-arginine in the diet.

After 4 days of therapy, the cycle of new eruptions was interrupted, the initial lesions regressed and there was an acceleration in the repair of larger lesions, which resulted in the improvement of the child's condition and comfort (Figure 1(A,B) and Figure 2(A,B)). There was complete resolution of the case after 2 weeks of L-lysine therapy.

The total cycle of PR was 4 weeks, from the first manifestation to complete healing of the lesions with residual white spots that disappeared in a few months with sunbathing.

L-lysine was administered for 30 consecutive days, always on an absolute fasting, being foods containing Arginine avoided.

3 | DISCUSSION

PR can be confused with other pathologies such as psoriasis, syphilis, allergic dermatoses, and fungi.[8] Even with spontaneous resolution, sunbathing helps relieve itching[2] justifying the indication of this therapy to the patient in this case.

The etiology of the disease is still unclear with the hypothesis that it is caused by viruses that could be reactivated[2,5,21] by other etiopathogenic agents as insect bites. Trauma would activate an inflammatory response that would trigger the disease typical rash[8] which would explain, in this case report, the main injury appeared days after the child suffered several bites.

One study evaluated the influenza virus subtype H1N1 as the cause of PR and ruled out this hypothesis,[21] excluding the possibility that the influenza vaccine, applied to the child in the previous month, may be the disease cause.

Human herpesviruses were also studied as possible causes of PR.[2,5,10,16] Divided into eight subgroups, HSV-1 and 2 or HHV-1 and 2 (HS virus), VZV or HHV-3 (varicella zoster virus), EBV or HHV-4 (Epstein-Barr virus), CMV or HHV -5 (cytomegalovirus) and three other viruses, the HHV-6, 7, and 8,[22] PR was strongly associated with reactivation of herpesviruses 6 and 7.[18,23]

HS viruses HHV-1 have also been suggested, but studies have not concluded a possible association with PR.[16,17]

In relation to HHV-6 and 7 viruses, antigens against HHV-6 were found on the skin of 17% of patients with PR while 67% had antigens against HHV-7 indicating a possible infection or reactivation of these viruses.[24]

Other studies suggest the possible reactivation of herpesviruses 6 and 7 associated with another viral etiology such as COVID-19 infection. Recently, skin manifestations have been reported in 0.2% of patients infected with COVID-19 in China and in 20% of patients in Italy. The most reported features were rash, urticaria, varicella-like vesicles, petechiae and acute childhood hemorrhagic edema. In Iran, a case of PR in a 27-year-old man was associated with COVID-19 infection. The medical history reported low fever, fatigue, gastroenteritis, and anorexia. After 3 days, an erythematous and scaly annular plaque appeared on the left forearm with new generalized papular lesions appearing throughout the trunk and upper extremities on subsequent days. A chest CT showed patchy ground-glass infiltration at the peripheral and base of both lungs consistent with the COVID-19 infection. The parents were infected with SARS-COV-2.[3]

The HHV-6 present two distinct variants with different immunological, biological, and genetic properties. HHV-6A is considered more cytolytic with a higher level of virulence, HHV-6B would cause the sudden rash (*Roseola infantum*),[25] which would explain a possible cause of PR in this case report, since the child was affected by roseola at 2-years-old and the HHV-6B, in its latent form, could have been reactivated[24,26,27] by insect bites.[8]

Another hypothesis would be that the child could have the latent HS virus (HHV-1), even without having had clinical manifestations like gingivostomatitis or cold sores, since the father has cold sores.[19,20] The latent virus reactivated by insect bites[8] could have caused the emergence of PR although this hypothesis has not been confirmed in studies.[16]

In recent years, several treatment options have been proposed to combat clinical manifestations of PR, including the use of antivirals.[28] Systematic reviews concluded that acyclovir was superior to placebo in controlling dermal symptoms and itching, helping with remission of PR by act to suppress viral replication.[29,30]

Another study showed that erythematous lesions of PR became less inflamed after 15 days of acyclovir, which started in the first days. New lesions were restrained, concluding that the antiviral presents better result if started in the first days of manifestation of PR, quickly controlling the symptoms and the disease course.[18]

Acyclovir is also widely prescribed at the onset of HS (HHV-1) lesions,[31,32] controlling the course of the disease as acting preventively in patients with recurrences, as well as the amino acid L-lysine.[19,20]

Consideration that acyclovir acts in PR[18,29,30] as well as in Herpes Labial with the same mechanism of action and effect,[31,32] and that the amino acid L-lysine has similar results to acyclovir,[19,20] it is suggested that L-lysine can act positively in PR.

L-lysine is one of the eight natural amino acids acquired in food or by supplementation. It plays a role in tissue repair, in the synthesis of growth hormones and in the production of antibodies.[33]

Patients followed for 12 months with recurrent manifestations of cold sores, from 4 to 12 episodes/year, received for 30 days 500 mg/day of L-lysine, in fasting, together with a reduction in the intake of L-arginine, another important amino acid in the diet. L-arginine is present in nut, gelatins, chocolate, raisins, and popcorn among many other food compounds. The protocol showed an average reduction of 49% in repair time of the lesions as a 63% reduction in the annual incidence of coldsores.[19] The same response pattern was maintained in patients followed for 8 years with greater reduction, both in the healing time and in the number of annual injuries, always controlling the lysine/arginine balance in the diet.[20]

L-lysine showed in vitro an effect in reducing the replication of the HSV-1 virus at a concentration of 0.7 mg/mL[34] and a gel composed of L-lysine, was applied to herpes lesions induced in rabbits showing a reduction in the lesions cycle, accelerating healing.[35] These studies demonstrate the positive effect of the amino acid against a virus of the herpesvirus family (HHV-1), supporting the results found in the use of L-lysine in this case of PR, reinforcing the possible association of PR with virus of the human herpesvirus family.

In one study, two adult patients (25 and 26 years old) affected by PR received 500 mg of L-lysine every 12 hours for 15 days, starting the treatment in an advanced phase of the disease (with an evolution of 3 and 4 weeks, respectively). After 21 days of treatment, there was a total remission of the PR.[36] In these cases, the cure occurred respectively 6 and 7 weeks after the beginning of the PR, and it is uncertain whether the remission would be caused by the use of the amino acid or the usual average PR evolution.[4] The ideal treatment would be using L-lysine to control viral multiplication, instituted at the beginning of the manifestations, with loading doses[20] to compete with L-arginine, an important amino acid for initial viral replication.[19,20]

The antiviral potential of L-lysine may also be associated with the fact that this amino acid increases the excretion of L-arginine by the kidney and intestine,[37] decreasing its concentration and consequently its action in the protein synthesis of the virus, preventing its replication.[38,39]

In vitro experiments have shown that arginine is associated with both replication and virulence of a variety of viruses.[40-42]

A patient with Herpes Zoster, another virus in the herpesvirus family, did not achieve the disease control with acyclovir since he received arginine supplementation during physical training, reinforcing the action of arginine in viral replication.[43]

It is known that a single virus particle (virion) cannot replicate or express genetic material (DNA, RNA) without the availability of amino acids. Amino acids play an important role in virus-related infections, as they are necessary for protein synthesis and regulate many metabolic pathways, including gene expression. The absence of essential amino acids can result in empty viral particles, free of nucleic acids.[44]

One of these amino acids is L-arginine, essential for the replication of some viruses and the progression of infections,[45] raising the hypothesis that it would be necessary for the formation of a functional protein essential for the virion maturation.[46]

Certain viruses remain in their latent form (inactive) and this characteristic is explained by the unavailability of arginine during stages of the infectious process. In the absence of arginine, the viral DNA synthesis is impaired, and the formation of virions is inhibited. However, when arginine is made available, rapid, and widespread reinfection occurs.[40]

The availability of arginine is necessary for the HS virus replication. The removal of arginine from the culture medium prevented the formation of virions while its addition immediately stimulated protein synthesis which was followed by the virus's formation. Cellular damage was evident in infected cells in the absence of this amino acid that is necessary for the expression of late viral functions related to the synthesis of proteins in the viral coating.[47]

Recently, PR was suggested as a cutaneous manifestation of Sars-Cov-2 infection.[3] Indeed, many dermatological diseases have increased during the COVID-19 pandemic. Among them, PR increased more than 2-fold (OR = 2.6; 95%CI = 1.2-5.3) during the pandemic period. In addition, PR could be an indicative for Sars-Cov-2 asymptomatic-carrier patients. The reactivation of HHV-6 induced by Sars-Cov-2 virus during the pandemic could also explain the increased in PR cases.[48] The role of L-lysine as complementary therapy for the PR manifestation in COVID-19 patients deserve future studies.

Since L-lysine supplementation is safe at the recommended doses and can influence the lysine/arginine balance, this therapy has been indicated for the control of HHV-1. A 70 kg adult could use between 800 and 3000 mg/day with good tolerance for side effects. However, higher doses (10-15 g per day) can cause gastrointestinal disorders such as nausea and diarrhea. A reasonable recommendation for supplementation would be between 500 and 1000 mg per day for prophylaxis, maintaining higher doses (3000 mg/day) for active outbreaks and only for a limited time, until the end of the acute phase. The use of 3000 mg/day of L-lysine for 3 days starting at the first signs of HSV-1 manifestations, may cause the initial lesions not to progress to the bullous phase disappearing in the prodromic phase.[20]

Patients with cardiovascular or gallbladder disease should be warned and alerted to the theoretical risks of long-term supplementation with L-lysine.[49]

4 | CONCLUSION

It is concluded, after the literature review, that PR is a disease with no definitive treatment because it still has a dubious etiology, however, with the supposed viral association, the proposal to treat clinical manifestations of PR with L-lysine supplementation and reduced food intake with the amino acid L-arginine, showed positive results in this case.

Further controlled clinical studies are needed to demonstrate the applicability of this therapy in the PR manifestation.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Maria Cristina Pedrazini - researcher responsible for monitoring the clinical case, data collection, bibliographic review and writing of the article. Francisco Carlos Groppo - researcher responsible for the final review of the writing of the article. All authors read and approved the final review.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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2.2 Pityriasis rosea - like cutaneous eruption as a possible dermatological manifestation after Oxford-AstraZeneca vaccine: Case report and brief literature review

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REVIEW ARTICLE

DERMATOLOGIC THERAPY WILEY

Pityriasis rosea-like cutaneous eruption as a possible dermatological manifestation after Oxford-AstraZeneca vaccine: Case report and brief literature review

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Abstract

Pityriasis rosea (PR) has been manifested in patients suffering from COVID-19 as well as after vaccine protocols against SARS-CoV-2. It has a possible association with the HHV-6B virus (*roseola infantum*) and can be controlled by antivirals such as acyclovir as well as by the amino acid L-Lysine that showed a positive result in reducing the number of lesions and healing time. The aim of this study was to report a case of PR after a second dose of Oxford-AstraZeneca, the adopted therapy and a brief literature review. A 53-year-old woman, phototype II, presented an erythematous lesion in the posterior right thigh 15 days after the second dose of Oxford-AstraZeneca vaccine. Eight days after the initial injury, new injuries appeared in the calf, buttocks and thighs. The diagnosis was PR with a 5-week eruption cycle. The treatment consisted of the use of L-Lysine, 3 grams loading dose and 500 mg for 30 days and moisturizing/healing lotion, starting 14 days after the herald patch. After the 5th week of the disease cycle, there were no new eruptions and the repair cycle continued for up to 8 weeks leaving some residual skin spots. It is concluded that the patient may be a carrier a latent virus, HHV-6, and the vaccine administration with immune system stimulation, would have activated the possible virus causing PR. L-Lysine helped to control the manifestation by limiting the number of lesions and their location, which were restricted to the legs, thighs and buttocks.

KEYWORDS
amino acid, AstraZeneca, human herpesvirus 6-7, L-Lysine, pityriasis rosea, vaccine

1 | INTRODUCTION

With the emergence of the current devastating pandemic, efforts joined in the search for vaccines that could reduce panic, socio-economic consequences and especially the circulation of the virus being the immunizing agents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the most important countermeasure to fight the pandemic, the coronavirus disease-19 (COVID-19).

Since December 2020, several effective vaccines against COVID-19 have been developed and approved in record time,[1-6] and numerous new vaccines are in the final stages of clinical trials.[7]

Several vaccines have been approved based on randomized, controlled, and blinded clinical trials. Among them are two messenger RNA-based vaccines: BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Modern) that encode the SRA-CoV-2 spike protein antigen encapsulated in lipid nanoparticles; the ChAdOx1nCov-19 (AstraZeneca) developed with a recombinant adenoviral vector from chimpanzee encoding the SRA-CoV-2 spike glycoprotein, the Ad26.COV2.S (Johnson & Johnson/Janssen) with a type 26 recombinant adenovirus encoding the spike glycoprotein of SARS-CoV-2 and, for emergency use in 22 countries, the inactivated vaccine against SRA-CoV-2 (CoronaVac).[8]

The ChAdOx1nCoV-19 (AZD1222) vaccine was developed at Oxford University, consists of a replication-deficient chimpanzee adenoviral gene (ChAdOx1) and contains the antigen gene, a SARS-CoV-2 structural surface glycoprotein (spike protein nCoV-19). In adults over 18 years of age, it was found to be effective against COVID-19 with a good safety profile in interim analyzes of ongoing clinical trials.[3] This non-replicating viral vector, the modified adenovirus, makes the immune system identify the spike protein, promoting a protective response against infection in case of exposure to SARS-CoV-2.[9]

What has been observed is that these vaccines have shown adverse effects in some people and among them are pain at the injection site, fever, headache, nausea and vomiting.[1,2] In some individuals there were skin reactions and among them there were reports of pityriasis rosea, 52 cases between January and June 2021.[10]

Pityriasis rosea (PR) is a benign skin disease, erythematous-squamous papules distributed on the trunk and extremities that starts, in most cases, with a single, oval, pink lesion called "mother patch" or "herald patch" showing a centrifugal growth measuring 2–10 cm in diameter. This lesion can remain isolated and single for 1 or 2 weeks when new secondary lesions of 0.5 to 1.5 cm appear in the thorax, abdomen, back and proximal extremities of the limbs. The initial phase is characterized by salmon-colored plaques, in the clinical phase a scaling begins and finally, the healing process is characterized by the lightening of the spots.[11–14] The evolution can vary from 6 to 8 weeks and can last from 3 to 6 months. Regression is spontaneous, leaving changes in skin color that disappear over the months. However, despite self-resolution, some dermatologists prescribe drugs such as antihistamines and corticosteroids, as well as sunbathing, which help when itching and with residual skin spots.[11,14]

Regarding etiology, fungi, bacteria and viruses were suggested, and the possibility of the involvement of autoimmune processes and pharmacological idiosyncrasies was also pointed out, however, some characteristics suggest that it is an infectious process which more recent trends attribute to a virus.[11,12,14–16]

Studies have shown a strong association of PR with human herpesviruses (HHV-6 and HHV-7) as an etiological factor[12,14–16] and with the suspicion of this viral involvement, therapy with antivirals such as acyclovir was indicated[15,17,18] as well as alternative therapy with L-Lysine amino acid[14,19] that showed positive results in reducing healing time as limiting the number of lesions when started at the beginning of the dermal manifestation, as soon as possible, still the first 2 weeks, in the viral multiplication phase.[14,19,20]

It is noteworthy that L-Lysine may also be associated with an increases excretion of an essential amino acid for some viruses initial replication, the L-Arginine.[21,22] Therefore, the use of L-Lysine together with a reduction in the intake of L-Arginine, present in supplements and foods such as chocolate, peanuts, nuts, gelatin, cashew nuts, corn, coconut, oats, coffee and raisins, can make difficult for the virus to enter in the cell remaining it in virion form limiting the evolution of the disease.[14,20]

Currently, PR has been associated as a dermal manifestation of SARS-COV-2 (COVID-19).[16,23,24] Although the diagnosis of PR has become more common during the COVID-19 pandemic, it is still unclear whether this cutaneous manifestation is secondary to the direct invasion of SARS-CoV-2, because in PR lesions the virus protein was found, whether it is due to reactivation of latent viruses such as HHV-6/7 and HHV-4 or EBV (Epstein–Barr virus) by the immunomodulatory capacity of COVID-19 to reactivates them or whether due to other factors.[16] Among the other factors is PR as a secondary reaction after vaccine protocols[25–31] being an important alert to dermatologists and other professionals in the area to assist in diagnosis.

In the midst of COVID-19 pandemic with several vaccine protocols being applied, the aim of this study was to report a case of RP after a second dose of Oxford-AstraZeneca, the adopted therapy and a brief literature review on the subject.

2 | CASE REPORT

A written consent form was obtained from the patient, aiming at reporting the case with unidentified photos.

Female, 53 years old, 61 kg, phototype II, with autoimmune disease diagnosed as Hashimoto's Thyroiditis using 125 mg levothyroxine sodium and without epidemiology for COVID-19, received the first and second dose of the Oxford-AstraZeneca vaccine in February 2021 and April 2021 respectively.

Eight hours after the first dose, she developed a 39-degree fever, joint pain, chills and headache, the latter remaining mild for 15 days. Fifteen days after the second dose of the vaccine, a reddish, erythematous lesion with mild itching was noticed on the posterior right thigh, above the knee joint (Figure 1). The patient thought it was a fungal lesion and self-medicating with a cream made up of ketoconazole (20 mg/g) + betamethasone dipropionate (0.64 mg/g), without noticing any improvement.

After 8 days the lesion was larger, measuring approximately 2 cm, with a scaly appearance and arising new smaller lesions in the calf, buttocks and thigh (Figures 2 and 3). An appointment with the dermatologist was scheduled 6 days after the secondary lesions, that is, 14 days after the initial lesion. The diagnosis was PR with suspension of the antifungal cream and prescription of a moisturizing, antiseptic and healing gel of 1.5 mg/g bismuth subgallate and 45.0 mg/g zinc oxide. An infectious disease specialist was also consulted confirming the diagnosis of PR as a reaction post-vaccination based on clinical characteristics and recent immunization history.

L-Lysine capsules were prescribed, a loading dose of 3 grams as a single dose, followed by 500 mg/day for 30 days starting 14TH days after the herald patch appeared. Restriction of foods and supplements containing the amino acid L-Arginine was also indicated. A few other lesions appeared in the following weeks, all limited to the lower limbs and buttocks, the last ones appearing in the 5th week on the left thigh (Figure 4A,B,C,D) and posterior left knee joint (Figure 5). At the end of 8 weeks, all lesions, only 12, were already in the repair phase, most of them with residual spots, as shown in Figures 1 and 2.

The patient had an undetected (negative) RT-PCR SARS-Cov-2 test, a total antibody the SARS-CoV-2 spike protein test—

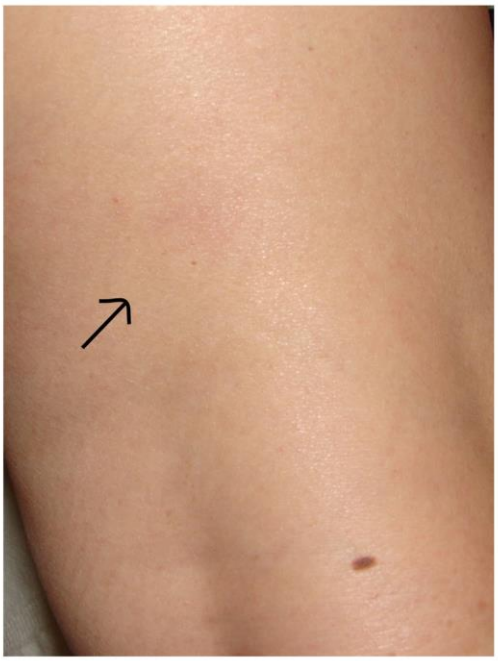

FIGURE 1 Herald Patch—7 weeks—right thigh—posterior knee

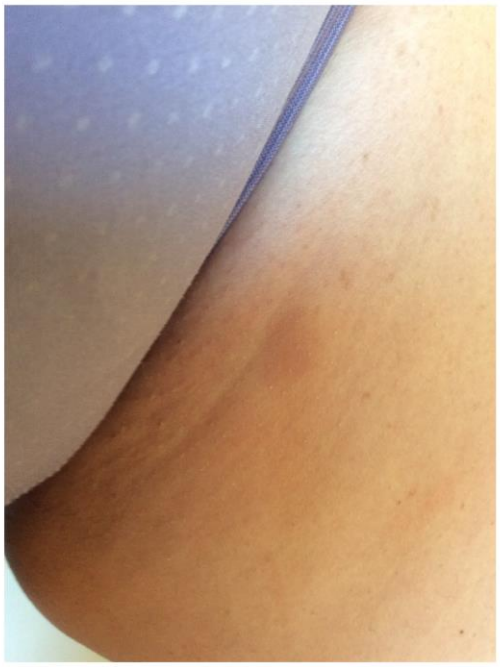

FIGURE 2 Lesion on the left thigh at 6 weeks

electrochemiluminescence method (positive)—67% (rv > 35%) and reported taking care of her daughter with roseola in 2008 and 2017 when the child developed the PR manifestation.

3 | DISCUSSION

The clinical case reported shows a skin reaction after a vaccine against the COVID-19 virus, diagnosed as PR despite the atypical condition, located only in the lower region of the trunk and lower limbs.

Dermoscopy has become an essential diagnostic tool in many diagnostic conditions in dermatology, such as melanocytic nevus lesions[32] however, in relation to dermoscopy in inflammatory skin lesions, knowledge is limited and there are few studies on the diagnostic technique of PR. Some authors investigated the dermoscopic features in PR lesions and the most common finding was collarette scale, which is also clearly visible to the naked eye. It was reported that many features that were not previously described for RP could be seen with the dermoscope, including irregular linear vessels, blood spots, brown blood cells and no brown structure, concluding that this exam can provide important clues to the diagnosis, especially in the atypical presentation of the entity.[33]

A punch biopsy could also be useful to check whether typical histological features of PR were present but both, dermoscopy or biopsy,

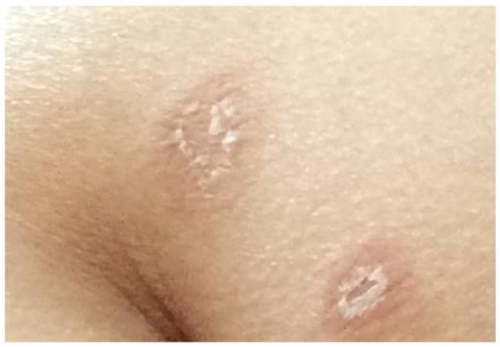

FIGURE 3 Lesion in buttocks at 2 weeks

were not indicated by the dermatologist or infectologist. They were categorical in the diagnosis of PR after collecting the clinical history and observing the injuries evolution.

Diagnosis of typical PR, with Christmas tree-shaped truncal involvement, is not difficult for doctors like dermatologists or general pediatrician however, its atypical presentations can be challenging even for these professionals.[13] In the typical form diagnostic doubts hardly arise but, as 20% of the cases present atypically, this can favor

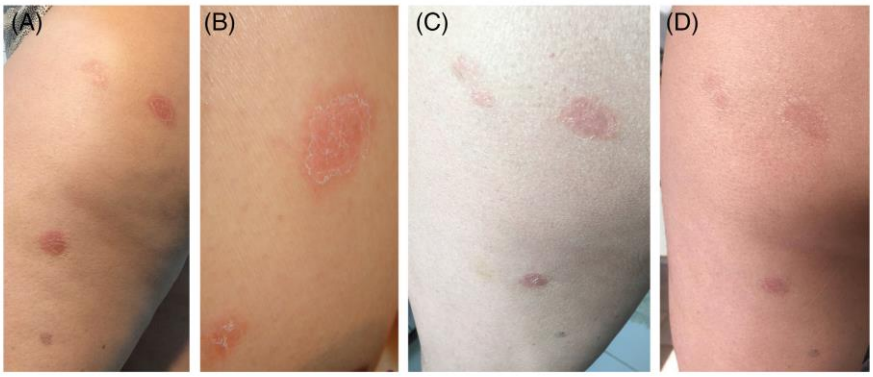

FIGURE 4 (A) Left thigh lesions at 10 days. (B) Larger lesion at 10 days. (C) Lesions at 14 days. (D) Lesions at 24 days

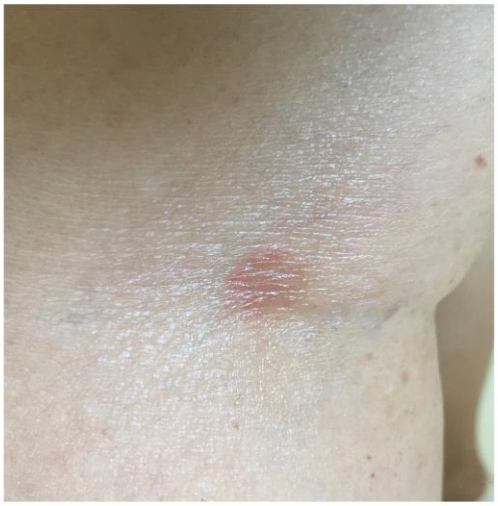

FIGURE 5 Lesion on the posterior left knee—10 days

unnecessary procedures and drug prescriptions.[34] Although it usually demonstrates a truncal predilection, this presentation may be absent in some patients who instead exhibit atypical features and distributions such as only lesions located in the extremities,[12] as seen in this case report. The fact that PR is also confused with other pathologies such as psoriasis, syphilis, allergic dermatoses and fungi[35] would justify the use of cream with ketoconazole and associations by the patient when the herald patch appeared.

Regarding the fact that the "mother patch" appeared soon after one of the doses of Oxford-AstraZeneca, there are other reports described of PR after other vaccine schedules, for example, against smallpox, tuberculosis, influenza, papillomavirus, poliomyelitis, tetanus, pneumococcus, triple viral (diphtheria-pertussis-tetanus), hepatitis B and yellow fever.[11] A report issued by the UK in June 2021 reports 52 cases of PR after Oxford-AstraZeneca vaccination in the first half of the year but does not give details of whether the reactions were after the first or second dose of the vaccine.[10] Other anti-SARS-CoV-2 vaccines also had PR as an adverse reaction[28–31] with the manifestation occurring after the first dose,[28] or after the second dose[28,30,31] and in some patients, the medallion (herald patch) and some lesions, occur after the first dose with exacerbation after the second dose.[29,31]

An international registry of cutaneous manifestations of SARS-CoV-2, established in March 2020, as collaboration between the American Academy of Dermatology and the International League of Dermatological Societies, was expanded on December 24, 2020, to collect information on reactions cutaneous with the use of vaccines against COVID-19. From December 2020 to February 2021, 414 skin reactions to the COVID-19 mRNA vaccines, Moderna (83%) and Pfizer (17%), were recorded. Delayed local reactions were the most common, followed by urticarial eruptions and morbiliform eruptions. Forty-three percent of patients with reactions to the first dose experienced recurrence after the second dose. Other less common reactions included the manifestations of herpes zoster, herpes simplex and PR-like reactions (PR-LE), these were present in 1 report after the first dose of Moderna, 2 reports after the first dose of Pfizer and 1 report after the second dose of Pfizer.[28]

Some authors differentiated between PR and PR-LE (like eruption or like reaction or post-drug/vaccine eruption) and inferred that there is a relevant importance in this distinction in order to assess the possibility of interrupting a medication or not. For them, typical PR can develop during but independently of therapy. If the manifestation occurs after the therapy start and in an atypical form (PR-LE), it is uncommon for the condition to resolve without interruption of treatment and it is suggested that the medication be discontinued if it is not extremely necessary, so that it is also avoid more dangerous skin reactions. According to the authors, the reactional PR-LE after the drug or vaccine would have a limited course, would disappear 14 days

after the drug was discontinued, and the mother patch would be absent, in addition to other characteristics. However, there are medications that act on the immune system, are indispensable and may favor the systemic reactivation of the latent human herpesvirus HHV-6/7 family virus.[36] Although the PR in this clinical case appeared after the vaccination schedule, it cannot be affirmed that it was a post-drug reaction exclusively (PR-LE) but rather a manifestation of viral activation, probably HHV-6, since the patient had contact with this virus in 2008 and 2017 while taking care of her daughter. The mother patch was present, and the cycle was 5 weeks of eruptions, characteristic of typical pityriasis rosea rather than pityriasis rosea-like eruptions according to the criteria defined by Drago et al.[36]

What can explain the emergence of PR in this clinical case is that an immune dysregulation induced by the specific infectious particles of the vaccine would have occurred, which would lead to the reactivation of the latent viruses.[37] This immune dysregulation mechanism is similar to what is observed in patients infected with COVID-19, also leading to other viral reactivations.[30] There is also the hypothesis of a less specific secondary reaction to the immune response as seen with other unrelated vaccines.[11,30] In a state of altered immunity, HHV-6/7 reactivation may result from a T cell-mediated skin-oriented reaction in an atypical presentation of self-limited PR.[27]

HHV-6 has two distinct variants with different immunological, biological and genetic properties. HHV-6A is considered more cytolytic with a higher level of virulence, HHV-6B would cause sudden exanthema (*Roseola infantum*).[14,38]

What would explain a possible cause of PR in this case report is the epidemiological factor. The daughter had roseola in 2008, becoming a latent carrier of HHV-6B and in 2017 she reactivated the virus with the PR condition. As the mother, patient in this case report, was exposed to the virus on these two occasions, it could have been transmitted while remaining latent and after the second dose of the AstraZeneca vaccine it was activated causing the PR manifestation.

The literature has shown several reports of cutaneous symptoms related both to the vaccination schedule against COVID-19 and related to the COVID-19 infection itself however, it is not yet known whether the SARS-CoV-2 virus or particles present in vaccines perform a role in the etiopathogenesis of dermatological diseases. A total of 0.8% of patients seen at a dermatology outpatient clinic between April 1 and May 15, 2019 presented PR cases, however, between April 1 and May 15–2020, 3.9% were cases of PR. After the pandemic, the number of patients with PR increased significantly, which may be related to HHV-6 reactivation.[39]

Cutaneous manifestations such as urticaria, chickenpox and acute edema have been reported in 0.2% of patients infected with COVID-19 in China and in 20% of patients in Italy. In Iran, a case of PR in a 27-year-old male has been associated with COVID-19 infection. Medical history reported fatigue, low-grade fever, anorexia, and gastroenteritis. After 3 days, an erythematous, scaly plaque appeared on the left forearm and other papular lesions appeared along the trunk and upper extremities on subsequent days. The parents were infected with SARS-CoV-2 and chest CT showed irregular ground-glass infiltration in the periphery and base of both lungs, consistent with COVID-19 infection.[23] and this year another study from February 16 to May 15, 2021, showed 405 reactions after vaccination with the BNT162b2 (Pfizer-BioNTech, 40.2%), mRNA-1273 (Modern, 36.3%) and AZD1222 (AstraZeneca, 23, 5%) of which 4.9% were from pityriasis rosea-like reactions[40] however, there are no reports in the literature until now about PR after the inactivated COVID-19 BIBP vaccine, developed by the China National Biotec Group (CNBG), Sinopharm.

The CoronaVac, another vaccine candidate against COVID-19 containing inactivated SARS-CoV-2, is a Chinese vaccine developed by Sinovac Life Sciences (Beijing, China). Randomized, double-blind, placebo-controlled clinical trials demonstrated the safety, tolerability and immunogenicity of this vaccine in healthy adults 18 years of age and older however, a case of pityriasis rosea in a patient following CoronaVac vaccination was reported. A 45-year-old female was received at the dermatology office with skin rashes which developed 4 days after the first dose of CoronaVac vaccine and it had been present for 1 week. The patient denied any history of allergies, recent infections, drug exposure or contact with anyone with COVID-19 infection. SARS-CoV-2 PCR tests performed from both the nasopharyngeal swab sample and the skin lesion biopsy were negative. The lesions faded within 3 weeks and 28 days after the first dose, she received the second dose and 4 days after, skin rashes were similarly reactivated at the previous lesion sites and faded within a week. The analyzes showed findings were consistent with typical pityriasis rosea rather than pityriasis rosea-like eruptions.[41]

In the last years, several treatment options have been proposed to combat the clinical manifestations of PR. In addition to topical antihistamines and corticosteroids,[11,14] antivirals such as acyclovir can also be indicated to control dermal symptoms, pruritus and to aid in the remission of PR by acting in the suppression of viral replication[17,18] however, for this to happen, it needs to be started in the first few days.[15] Another alternative treatment for PR would be the use of L-Lysine 3 grams for up to 3 days, loading dose, followed by 500 mg/day for 30 days[14,19] also starting in the first days of the manifestation of PR.[14] The antiviral potential of L-Lysine may be associated with the fact that this amino acid increases the excretion of L-Arginine by the kidney and intestine, decreasing its concentration and consequently its action on protein synthesis by the virus, preventing replication,[14,21] and that the lesions do not progress to the active clinical phase, disappearing in the prodromal phase.[14,20]

To avoid the reactivation of latent viruses of the herpesvirus family is important the lysine/arginine balance in the diet. To control the multiplication of the virus, when active, an increase in the supply of L-Lysine and a reduction in the intake of L-Arginine are indicated.[14,20] The fact that the patient in this report started L-Lysine with reduced L-Arginine intake, 14 days after the medallion appeared, may have contributed to the reduced number of lesions limited to the thighs (5), calf (1), posterior knee (1), and buttocks (5).

It has been suggested that during the COVID-19 pandemic, large-scale epidemiological studies should be conducted to elucidate whether there is in fact a relationship between vaccination regimens and the reactivation of latent viruses.[37] This mass investigation would be important to see whether this reactivation could be a coincidence

or a consequence, either in relation to reactivation by COVID-19 infection or by the anti-SARS-CoV-2 vaccines.

Overall, the data support that skin reactions post-immunizing agents anti-COVID-19 are generally non-hazardous and self-limiting and should not discourage vaccination. So far, there are no reports of patients who have experienced anaphylaxis or other serious adverse events.[28] Health professionals should be aware of these adverse reactions to the vaccine, carry out the appropriate management.[29] and reinforce with patients about the potential benefits of receiving immunizations, even if small reactions occur.[28]

4 | CONCLUSION

It is concluded that even if there are dermal reactions after vaccination against COVID-19, as they are not dangerous, patients should be advised to receive necessary doses, regardless of the immunizing agent.

PR is a benign, self-limiting disease, with spontaneous resolution and without a definitive treatment protocol, but with the supposed viral association, antivirals can be indicated and among them there is the proposal to use the amino acid L-Lysine with positive results.

Health professionals should be aware of the possibility of PR as a symptom of COVID-19 as well as a reaction to vaccines and provide the necessary counseling.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Maria Cristina Pedrazini: researcher responsible for monitoring the clinical case, data collection, bibliographic review and writing of the article. **Mariliza Henrique da Silva**: researcher responsible for diagnostic confirmation, technical information, bibliography reviews and support in writing; final article review. All authors read and approved the final draft.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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2.3 L-lysine: its antagonism with L-arginine in controlling viral infection. Narrative Literature Review

Artigo submetido ao periódico BJCP – British Journal of Clinical Pharmacology (Anexos 4 e 5)

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Literature Review – Area of Pharmacology / Therapy / Infectology / Virology

Title: L-lysine: its antagonism with L-arginine in controlling viral infection. Narrative Literature Review.

Short Title: L-lysine and L-arginine in viral infection

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What is already known about this subject and what this study adds.

The first studies with these amino acids date back to the 1960s, where it was inferred that, in vitro, lysine could suppress the expression of viruses such as adenovirus and herpes simplex virus. Over the years, other authors have written about their in vitro experiments with other viruses as well as published their clinical studies. Doubts and criticisms arose and in this work, we bring a major review uniting the aspects of some viruses, where and how amino acids can interfere with viral multiplication, the first studies conducted with the coronavirus and our experience with the use of lysine and suppression of arginine against herpes simplex as in another herpesvirus, the roseovirus. We unite a lot of information in a single work that can call the scientific community for new studies with amino acids, prophylaxis and therapy, in the war against viruses.

ABSTRACT

Knowledge about viral characteristics, mechanisms of entry into the host cell and multiplication/dissemination can help in the control and treatment of viral pathologies. Several nutritional factors linked to the host may favor viral multiplication and their control, may lead to new prophylactic alternatives and/or antiviral therapies. The objective of this review is to discuss the relationship between the amino acid L-lysine and the control of viral infections, aiming at a possible therapeutic property. This research used databases such as PubMed, Web of Science, Scielo, Medline and Google Scholar, as well as searching for articles cited by journals. Textbooks were also included in the absence of information in the cited articles. The time frame covered the period between 1964 and January 2022. The observed studies have shown that the usual antiviral therapies are not able to interfere with the viruses in their latent state, however, they can interfere with the adhesion and fusion of viral particles or the formation of proteins, which play an important role in viral epidemiology and control, particularly in the initial moment and in the reactivation. Lysine is an amino acid that can interfere in some of these phases by antagonizing another amino acid, arginine, and also by promoting the increase of arginase, increasing the catabolism of arginine, which is an essential amino acid for some viruses. Although there is evidence of the importance of these amino acids in viral control, more studies are needed, with a view to new antiviral therapies.

Keywords: L- lysine, L- arginine, Virus, Human herpesvirus, Amino acids, COVID-19

1 INTRODUCTION

Viruses, viroids, virusoids and prions are intracellular parasites unable to complete their replication cycle outside a host cell.[1] They have high replication speed promoting high mutations rates with changes in structural components and enzymes, causing increased drug resistance.[2]

They are the smallest infectious agents with diameters ranging from 20 to 1200 nm, with different shapes (icosahedral, helical, rectangular or complex) and, capable of infecting plants, animals and bacteria, in addition to humans.[3]

According to their genome, they are classified as RNA viruses with multiplication in cellular cytoplasm e.g., coronavirus, influenza virus and retroviridae (Fig.1) or DNA viruses with intranuclear multiplication e.g., herpesvirus, adenovirus and hepadnaviridae (Fig.2). The nucleic acid (DNA or RNA) is surrounded by the capsid that is formed of capsomers (glycoproteins). The set (capsid + macromolecule) is called nucleocapsid and, some viruses also have the integument, a non-structural proteins important for another structure formation, the viral envelope that is formed by viral proteins and proteins from host plasma membrane that is carried during the virus exit from the cell (Fig.3). It is the viral glycoproteins of the nucleocapsid or envelope, in the case of enveloped viruses, that play an important role in interacting with receptors on the target cell.[4]

Herpesviridae family is composed of more than 100 double-stranded DNA viruses that infect animals and humans, but only eight infect humans.[5] There is still an aggravating factor related to this family, herpesviruses become latent and can be reactivated causing morbidity and infecting a large percentage of the population [6] resulting in lifetime transmission.

In the last two decades, several antiviral agents have been developed and, the therapeutic choice is limited by the level of efficacy and toxicity. However, viral infections are still a significant cause of worldwide mortality.[5]

Knowing the viral characteristics, the behavior of entrance into the host cell, the multiplication and dissemination mechanism, may help to control the perpetuation of these infectious agents. Some nutritional factors, linked to the host, may also favor viral multiplication and may constitute new prophylactic and/or antiviral therapeutic alternatives. The objective of this review is to discuss the relationship between the amino acid L-lysine and the control of viral infections, aiming with a view to a possible

therapeutic property.

2 METODOLOGY

Descriptive review with scientific productions indexed in the following electronic databases: PubMed, Web of Science, Scielo, Medline and Google Scholar. In addition to scientific articles, textbooks were also included in the absence of information in the cited articles. The time frame covered the period between 1964 and January 2022. The selection of articles was based on the analysis of abstracts, including those that contained as descriptors "Virus", "Herpesvirus", "Coronavirus", "SARS-CoV -2", "Viral Reactivations", "Viral Replication", "Antivirals", "Latency", "Amino Acids", "Pharmacology of Amino Acids", "L-Lysine" and "L-Arginine" and the relationship between them.

3 REVIEW

3.1 – Human Herpesvirus

There are eight viruses from the Herpesviridae family that parasitize humans, and almost 100% of the adult population has been infected with at least, one of them. Herpes simplex viruses type 1 and 2 (HSV or HHV-1/2), varicella zoster virus (VZV or HHV-3), Epstein Barr virus (EBV or HHV-4), cytomegalovirus (CMV or HHV-5), roseovirus (HHV-6/7) and oncovirus (HHV-8) and among the oncoviruses, KSHV is responsible for Kaposi's sarcoma.[7]

They are spherical, enveloped and have linear double-stranded DNA, containing from 70 to 170 genes, of which 43 were inherited from the same ancestral herpesvirus. They are highly adapted to their hosts [8] and a symbiotic relationship would be discussed since studies have inferred that there is a systemic activation of macrophage, induced by the prolonged production of interferon-gamma in response to viral infections, which could promote host protection against some bacteria. This symbiotic relationship would be a coherent hypothesis, as it would promote the host against some opportunistic invaders and, consequently, the virus itself, which would maintain its invasion.[7]

Herpesvirus infection begins with its entry into the host cell by fusion with the cell membrane or by endocytosis, but some viruses can reach both ways.[9] The

interaction between cell receptors and viral envelope proteins promotes the first step, adsorption. Then, there will be the fusion (viral envelope / cell membrane) and finally nucleocapsid penetration that is transported through the cytoplasm until it finds a nuclear pore where the genome is released [8] in the nucleus (Fig.2) through the portal vertex (Fig.4), an essential capsid protein in the viral packaging that start during the transport of the daughter viruses through the cytoplasm of host cell. Small therapeutic molecules target the portal vertex of HSV and VZV with the aim of preventing viral dissemination by inhibiting packaging.[10, 11]

Viral transcription is complex and will occur in the form of cascades after DNA injection into the nucleus. Early genes will encode regulatory functions, DNA replication and a variety of proteins involved in modifying host cell metabolism or immune responses. Late genes will mainly code for viral proteins. Viral DNA synthesis occurs by through a replication mechanism in which genomes are cleaved, enclosed by capsids and released into the cytoplasm. In the Golgi compartment, proteins present in the viral tegument, including the vertex portal protein, will initiate viral packaging. When leaving the cell by pinocytosis (budding), the cell membrane proteins will be loaded giving rise to mature virions that will continue to infect new cells.[8, 12] (Fig.2)

Being packaged viruses that normally sprout from the cell membrane, this means that cell lysis is not necessary, however, active production of viral particles in epithelial cells or leukocytes can normally result in cell death.[7]

After primary infection, these viruses establish lifetime latency where viral gene expression will be limited.[8] Some factors contribute to the maintenance of latency, while others will contribute to its disruption and consequent reactivation of viral replication.[7]

3.1.1 – Latency

In healthy individuals, the primary infection is usually inapparent, meaning that many infected people are unaware of the occurrence of latent virus. Herpesviridae subfamilies were classified based on genomic and tissue latency predilection characteristics. Alpha-herpesviruses are neurotropic and become latent in the dorsal root ganglia. When reactivated, they cause localized epidermal ulceration (herpes simplex types 1 and 2) or spread across several dermatomes (varicella-zoster virus). Human cytomegalovirus, the prototype of beta-herpesvirus, establishes latency in bone marrow-

derived myeloid progenitor cells. Gamma-herpesviruses are lymphotropic (Epstein-Barr virus), maintain latency in B cells and when reactivated they produce several neurological complications.[13] Details of human herpesviruses' family are described in table (1).

To establish and maintain latency, a virus depends on epigenetic mechanisms of the host for the silencing of viral genes, which is achieved by packaging the DNA in certain types of histones. During latency, when the cell enters mitosis, viral DNA and chromosomes are copied by the action of DNA polymerases. This is important for the virus to remain present in the long-term, as some of the daughter cells will die. The production of viral proteins is also minimal to avoid immune surveillance.[7]

The HHV-1 is considered one of the most frequent pathogens acquired by humans and that are in latency. Statistics show that 50% to 90% of individuals worldwide are seropositive for this virus. Human herpesvirus infections are endemic and transmission occurs through direct contact with an infected person, either through contact with the lesions, contact with saliva, sexual contact, with blood or direct contact with utensils used by the infected person. Primary HHV-1 infection usually occurs in childhood and 90% of them are subclinical. The most frequent oral clinical manifestation related to the herpes virus type-1 is herpetic gingivostomatitis, which causes fever, irritability, pain on swallowing, regional lymphadenopathy and several ulcerated lesions spread over the oral mucosa, lips and nose. In adolescents, the primary contamination may manifest itself only as a sore throat and in 10% of infected people, the first manifestation may be associated with only a mild case of flu or be asymptomatic. Incubation has a short period, about one week. Then the virus is not eliminated by the immune system, entering the neurons and going to the ganglia where it will maintain the latency state. When reactivated, they can cause lesions with the appearance of watery blisters in some places such as the orolabial skin, nose wing, tongue, lips, genitals, buccal mucosa and hard palate.[14, 15]

Both, HHV-1 and HHV-2 (genital herpes), have co-evolved with humans for thousands of years and are present in high prevalence in the world population. They can be in both the oral cavity and the genital area, and are also responsible for blindness (herpetic keratitis) and potentially fatal encephalitis in immunocompetent and immunocompromised individuals of all ages. The latency and reactivation capacity in healthy individuals is likely given by the numerous virulence factors these viruses have evolved to evade the host's antiviral responses.[16]

Another virus that has drawn attention with its emergence from latency during the COVID-19 pandemic is HHV-3 or VZV (varicella zoster) with its consequences and morbidities for patients.[17, 18] When reactivated, in addition to dermal involvement, it can also compromise the ocular mucosa with corneal sequelae and must be controlled to avoid blindness.[19, 20]

HHV-6/7 (Roseovirus - Subfamily Beta) has also been drawing attention during the COVID-19 pandemic. Causer of the sixth disease (roseola infantun or exanthema subitum), after a long latency period, it can be reactivated in association with SARS-CoV-2 or by the COVID-19 vaccine, causing an erythematous papular squamous disease called pityriasis rosea (PR).[21] Like all herpesviruses, HHV-6/7 establishes lifelong latency where viral genome expression is limited but is delivered to daughter cells without the production of infectious virus. Latency occurs in primary lymphoid tissues (medulla and thymus) as well as in secondary MALT tissues (mucosa and skin). The proposed site is the monocyte which once it enters a tissue differentiates into a macrophage. In vitro studies also have suggested bone marrow progenitor cells and T cells (CD4+) as well as astrocytes (Table 1).[22]

These viruses can remain in their latent form for a long time and in vitro studies with HHV-1 have suggested that the latent state is closely associated with the of amino acids' availability.[23, 24]

In the population, there are individuals with the susceptibility to be infected by at least one member of the herpesvirus' family, as can be those infected by more than one. They will remain in a latent form until, at some point, they can be reactivated by triggers.[21, 25-27]

3.1.2 – Viral Reactivation

Reactivation is a dangerous option for the virus because during replication, DNA polymerase (DNA virus) takes over viral multiplication and several other host mechanisms will be activated, including its immune system or its internal signaling, leading the cell to death. Reactivation does not necessarily imply clinical symptoms as this will depend on the immune response and the level of viral production.[7]

In vitro studies showed that the availability of the amino acid arginine could lead to virus reactivation [23, 24] and since this amino acid is in high concentration in some foods such as peanuts, cashews, almonds, granola and chocolate [28-30] (Fig.5) (Table 2), a

dietary imbalance could stimulate viral replication in latent viruses carriers, suggesting that these foods should be avoided, giving preference to those with a lower concentration of this amino acid.[25] (Table 2)

There are several triggers that can reactivate herpesviruses and among them are specific hormonal conditions, stress, weather conditions such as cold and solar radiation or conditions in which depression or activation of the immune system occurs.[30]

The local trauma, insect bites,[26, 30, 32] pharmacological idiosyncrasies and genetic susceptibility [32, 33] have also been cited as triggers. It is important to consider that some medications that act on the immune system can cause reactivation, however if essential, they should not be interrupted. [21, 34]

Factors such as oncogene, hypoxia and viral infections are on the list of possible triggers for viral reactivation [35] and the last two conditions, hypoxia and viral infection, are present in COVID-19 explaining the possible HHV-1/2 [36, 37] or HHV-6/7 [38] reactivation in SARS-CoV-2 infected patients.

Reactivations can be caused by both, local and systemic factors,[39] by an immunosuppressive viral mechanism [37] or even by the simple immune dysregulation caused by a virus.[40]

In patients immunocompromised by COVID-19, reactivation of herpesvirus' family, including HHV-1/2/3, would result in further damage and may have clinical as well as prognostic implications.[41]

Since the beginning of the SARS-CoV-2 pandemic, cases of oral manifestations including herpes simplex have also emerged even before the manifestation of the COVID-19 disease itself [42] as were also considered as the only symptom of SARS-CoV-2 infection, suggesting a possible relationship between the presence of herpetic infection together with a latent form of COVID-19.[41]

PR was also associated with the first manifestation of COVID-19 [43] or as a manifestation associated with other signs of the disease, however, it is still unclear whether this cutaneous manifestation is secondary to the direct invasion of SARS-CoV-2, if it is due to latent HHV-6/7 reactivation or if due to other factors.[38]

Immune dysregulation created by vaccines may also play a role in reactivating latent infection.[44, 45] The humoral response distraction due to vaccination, can lead to loss of immune control latent virus [46] however, no vaccination schedule should be discouraged because it causes reactivations that are often controllable.[21, 27]

In 2021, there was an increase in PR-like reactions after SARS-COV-2 vaccines

due to the possible HHV-6/7 reactivation. The altered immune status would provoke a T-cell mediated skin reaction [18, 47] causing the rash, however, there are reports of PR after other vaccines, e.g., against smallpox, tuberculosis, influenza, papillomavirus, poliomyelitis, tetanus, pneumococcus, MMR (diphtheria-pertussis-tetanus), hepatitis B and yellow fever.[48-50]

There was also an increase in cases of herpes simplex and herpes zoster after anti-COVID-19 vaccines,[27, 40, 51-53] reinforcing the hypothesis of immune dysregulation or immunomodulation that can also be caused by other vaccines such as trivalent influenza, H1N1, hepatitis A and rabies vaccines.[36]

The mechanism of the immune response to vaccines, which would lead to the reactivation of other viruses, is still not fully elucidated. The main hypothesis would be that herpesvirus reactivation would result from failures in the innate or cell-mediated immune response, initiated by vaccination.[37] Immune dysregulation, caused by specific infectious particles in formulation of the immunizing agent, was also identified as a possible cause of viral reactivation. It has already been suggested to develop more epidemiological and larger-scale studies during the COVID-19 pandemic to verify the relationship between latent virus reactivation and different vaccine regimens. [44]

What can be seen from these studies, is that these triggers cause both physical and psychological stress and in individuals with latent virus, may be sufficient to disrupt the delicate balance between viral activity and immune response.

The viral manifestations reported here such as pityriasis rosea, herpes zoster, and herpes simplex can be treated and controlled with antivirals such as acyclovir, a protease inhibitor.[20, 54, 55] In the case of herpes simplex, in addition to acyclovir, other protease inhibitors, virus fusion inhibitors or nucleoside analogues can be used. Some of which are reserved for immunocompromised patients with severe herpes simplex.[15, 31, 55]

3.1.3 – Antiviral therapies

Pharmacology plays an important role in the production of antivirals and the pharmaceutical arsenal to fight viruses is immense however, unfortunately these drugs cannot rid an organism of the herpesvirus.[7]

The main drugs used in the treatment of infections by the herpesvirus' family are the acyclic guanosine analogues such as Acyclovir (ACV), Valacyclovir (VCV), Penciclovir (PCV), Famciclovir (FCV), Ganciclovir (GCV) and Valganciclovir

(VGCV), in addition to the cytosine analogues (Cidofovir) and the pyrophosphate analogue (Foscarnet).[56, 57]

The first antiviral used against HHV-1/2 viruses was Idoxuridine, a nucleoside analogue capable of inhibiting viral nucleic acid synthesis, but due to systemic toxicity its use was limited.[58]

Acyclovir is one of the most prescribed antivirals for the treatment of herpesvirus manifestations [19, 20, 25, 26, 59, 60] being considered gold standard.[61]

Even though some studies have shown the lack of prophylactic or preventive treatment efficacy with acyclovir, others suggest that this antiviral may be beneficial as a curative treatment mainly in herpes simplex virus reactivation in intensive care unit patients where the infection starts in the throat after 3 to 5 days of hospitalization and then progresses to the respiratory system to reach the lung in 7 to 10 days, increasing morbimortality.[62] In times of a COVID-19 pandemic, this information is important.

The onset of herpes simplex-associated pneumonia should be considered in the immunocompromised patient and/or the intensive care patient, who continues to worsen despite adequate treatment for the pneumonia. It is also important to consider, even if the value of prophylactic treatment with acyclovir has not been proven, the use of the prophylactic antiviral in these special patients.[63, 64]

Acyclovir is also the drug of choice to control pityriasis rosea (HHV-6/7) in more severe cases or when itching, number of lesions, or time of onset are desired.[59, 60]

This antiviral, like other antivirals, acts in the early stages of viral replication and the success of therapy can be compromised if therapeutic intervention does not occur during the early stages of infection to prevent replication and evolution of signs and symptoms.[21, 27, 60]

Therapy started during the active period of the infection or its eventual discontinuation, are factors that reduce the effectiveness of the treatment as well as increase the risks of the emergence of resistant strains, which affects more immunocompromised patients (2.5-25% of resistant strains) and a lower percentage of immunocompetent ones (0.3-0.7%).[65]

Studies have shown that some viruses controlled by acyclovir, HHV-1 and HHV6/7, could also be controlled by the amino acid L-lysine, leading to the conclusion that this amino acid could be used as an alternative therapeutic with promising results. The prophylactic or therapeutic protocol with L-lysine proved to be effective in reducing the number of lesion (HHV-6/7), number of annual reactivations (HHV-1),

their severity as well as the healing time of active lesions (HHV-1/6/7). The initial doses or even the loading doses, when faced with a reactivation, must occur in the initial phases of viral replication together with the control of the supply of the amino acid L-arginine.[21, 25-27]

3.2 Amino acids

There are 20 common amino acids called *a*-amino acids. They have a carboxyl group (COOH) and an amino group (NH2) attached to the same carbon atom (C). Furthermore, they differ from each other in their side chains or R groups that vary in structure, size and electric charge, influencing solubility in water. They are grouped into five main classes based on the properties of the R group, particularly with respect to their polarity or tendency to interact with water at biological pH (close to 7). The polarity of the R group ranges from nonpolar and hydrophobic (not water-soluble) to highly polar and hydrophilic (water-soluble). The polar R group can be further divided into uncharged, negatively charged (classified as acidic polar) or positively charged (basic polar). In addition to these 20 amino acids, there are others that are less common.[66] Among the basic polar amino acids, there are two that will be discussed in this chapter and throughout the text (L-lysine and L-arginine) and which structurally and in terms of pharmacological characteristics, are very similar (Table 3).

Due to pKa above 10 in the R chair, both L-lysine and L-arginine assume a protonated (cationic) condition at neutral pH. They are present in all ingested proteins and are classified as proteinogenic [66] however, each is in different amounts in each protein, and the presence of one good may be superior to the presence of the other. As an example, we have chocolate, peanuts, wheat flour, cashews, granola and almonds as the champions in terms of arginine in relation to lysine, while in the vast majority of proteins, lysine is superior to arginine.[28-30] (Table 2)

L-lysine and L-arginine are structurally related molecules and may compete, during absorption from the intestine, for the same carriers as well as during transport across cell membranes. In addition, the cell can become saturated in one of them, slowing its absorption, leaving the other free to be absorbed more.[67] This information is important for understanding the dynamics of lysine/arginine in the antiviral balance.

3.2.1 L - arginine: pharmacological aspects

L-arginine (L-Arg) is L-2-Amino-5-guanidinovaleric acid, a common natural constituent in the human diet and readily available in some foods of animal and plant origin.[68]

Like all amino acids, it is absorbed in the small intestine, metabolized in the liver as in other tissues and its metabolites can be excreted by the kidney or used for the anabolism of other substances, including new arginine. It is considered a semi-essential amino acid because it is obtained from the diet or produced in the mitochondria of hepatocytes through the complete or partial urea cycle.[69, 70]

Metabolic, therapeutic and viral activities.

In addition to its important role in the formation of essential proteins, arginine is a substrate for the various isoforms of nitric oxide synthase (NOS) that will convert arginine into nitric oxide (NO) and citrulline. In the urea cycle, arginine is converted by arginase (ARG1) to ornithine and urea, thus allowing the renal excretion of excess nitrogen produced by protein catabolism. The urea will also be excreted by the kidneys while the ornithine will travel to the mitochondria where it will be recycled, restarting the urea cycle to remake arginine. Citrulline and ornithine, as direct products of arginine metabolism, undergo modifications in other bioactive compounds.[69, 70]

The NO formed from arginine, is present in the endothelium and is a potent vasodilator. Individuals with arginine malnutrition and with certain physical conditions such as hypertension or diabetes may be advised to supplement L-Arg in safe amounts. Epidemiological studies have already shown that L-Arg has protective effects on the cardiovascular system, improving endothelial function and reducing blood pressure.[68]

Interestingly, the functions of NO are complex and antagonistic. While it has important functions as a messenger in the bronchopulmonary, cardiovascular, neural and renal systems, excess NO is considered toxic to cells. It plays an important role in the action of macrophages in the face of inflammatory processes, however, there is a fine line between the non-toxic concentration for host cells and the toxicity necessary for its antimicrobial action. Depending on the concentration and the tissue on which it is acts, this molecule will present a marked aspect of being beneficial or potentially toxic. Some authors have described NO as a “double-edged sword” [71] and in this concept, arginine, precursor of NO, could have a positive action in the face of inflammatory

process as well as a negative one being able, indirectly, to damage tissues.

Arginine also seems to have an antagonistic action with the amino acid L-lysine. Patients with lysine-related inborn errors of metabolism such as pyridoxine-dependent epilepsy (PDE) and type 1 glutaric aciduria (GA1), follow a lysine-restricted diet with lysine-free amino acid formulas fortified with arginine. Oral supplementation with arginine is the newest therapy for PDE because of this lysine antagonism.[72, 73]

It is considered a conditional amino acid that becomes essential for the development of babies, children or adults and its supplementation is widespread in the fitness community because its inherent properties can increase performance and muscle hypertrophy, especially when combined with other nutrients however, it can be an aggravating factor in viral control. Patients using arginine supplementation to improve physical training were affected by recurrences of herpes zoster that were previously controlled by antivirals, however, in view of supplementation with the amino acid, control was not achieved until the use of the supplement was suspended, as was control of food intake.[19, 20]

It is known that a single virus particle (virion) cannot replicate or express genetic material (DNA, RNA) without the availability of amino acids. These substances play an important role in virus-related infections, being necessary for protein synthesis and regulation of metabolic pathways, including gene expression. The absence of amino acids essential to the virus, such as arginine, can result in empty viral particles, free of nucleic acids,[23, 54] or naked particles, without capsid, with the DNA exposed to the DNases of the nucleus.[24] The consequence is the generation of non-mature viruses, without viral action.

Arginine depletion has been investigated as a potent antiviral strategy against Herpesviridae family (HHV-6/7[26], VZV[19], HHV-1[25]) and against Adenoviridae family.[75, 76]

Several other arginine-dependent viruses, RNA and DNA, were topic of discussion, e.g., cytomegalovirus (CMV), influenza A, vaccinia, SV-40, measles virus, Marrek's disease (MDHV), hepatitis C (HCV) and SARS-CoV-2,[70, 77] on the positive effect on viral control with amino acid depletion however, in an arginine-deprived environment, this amino acid is generated endogenously from ornithine in the urea cycle,[70] which shows the complexity of studies with amino acids.

In vitro experiments reinforce the association of arginine in both, replication and virulence of a variety of viruses,[23, 78, 79] and it is essential for the progression and

severity of infections. Investigations that led to the conclusion that arginine would be necessary for the formation of a functional protein essential for virion maturation,[75] justify further studies with this amino acid and its possible antagonists.

Certain viruses are characterized by remaining in their latent (inactive) form, this characteristic being explained by the unavailability of arginine during various stages of the infectious process. In the absence of arginine, viral synthesis is impaired and the formation of complete viral particles is inhibited. When arginine becomes available, rapid and widespread reinfection occurs.[23]

The availability of arginine is absolutely necessary for the replication of the herpes simplex virus in several stages, especially the late stages such as capsid formation but, according to some authors, it does not interfere with DNA synthesis [24] however, when adenovirus was used, arginine withdrawal also influenced DNA formation in addition to capsid formation.[76]

For the control of viral activity, this will only be achieved if the removal of arginine takes place during the initial stages of the replication process, that is, between 6 and 20 hours post-infection.[75, 76, 80] If the amino acid is available during these first moments it can cause, in addition to increased viral synthesis, a greater progression and severity of the infection.[23] This information reinforces the protocol for starting the use of the amino acid L-lysine, which competes with arginine, in the early stages of infection.[21, 25-27]

The herpes simplex virus has nine proteins in its envelope and in the capsid, there are two more and one of them (protein VII) is very rich in arginine and its depletion can generate naked viruses.[81]

The hypothesis of arginine viral activity was reinforced when, in culture medium, the removal of this amino acid led the virus to a latent state. When reintroduced, multiplication resumed with the appearance of an almost synchronized infection. Resumption of viral multiplication was immediate only if arginine was reintroduced into the culture medium before 7 days. If it happened on subsequent days, there was a delay directly proportional to the time of deprivation. There is, according to this study, a threshold concentration of arginine and a limited time interval for HSV replication,[82] which may suggest that the control of this amino acid in the diet, at least during the phases of viral multiplication, would be enough to control the infection.

Just like the herpes virus has an arginine-dependent protein in its capsid,[81] in the case of SARS-CoV-2, the “spike” protein of the virus crown is also dependent on this

amino acid.[77]

It is the spike protein that mediates virus entry into host cells and this protein harbors an S1/S2 cleavage site essential for cell/cell lung infection, a different mechanism for this pandemic virus. Interestingly, this site, which is so important for cell/cell infection, is also arginine-dependent, and this has not been seen in other coronaviruses. Because this multibasic S1/S2 cleavage site is arginine-dependent and essential for SARS-CoV-2 infection in humans, this region would be a potential target for therapeutic intervention.[83]

Some patients with severe manifestation of COVID-19 have participated in clinical trials where studies focus on direct antiviral therapies or immunomodulation. It has been argued that a therapeutic approach to be investigated clinically is to disruption the host-virus relationship through amino acid restriction, a strategy successfully used in the context of cancer treatment and arginine depletion may be an effective therapeutic approach against COVID-19 as it appears that this amino acid is also important for the successful SARS-CoV-2 replication in addition to being an important substrate in the exacerbated host inflammatory response due to NO formation by macrophages. In view of this, the reduction of arginine could also attenuate the severe inflammatory response of COVID-19, suggesting the control of arginine with the use of enzymes similar to arginase.[70]

One study did just that using pegylated recombinant human arginase I (peg-ArgI). The use of this enzyme in culture media showed an anti-herpetic activity in vitro. Arginine catabolic enzymes can modulate deleterious sequelae associated with viral diseases, controlling virus replicative processes and representing a new pharmacological approach. Herpesvirus tests showed that the enzyme inhibited viral replication, infectious virus production, cell-to-cell spread/transmission, and virus-mediated cytopathic effects [84] however, it has already been discussed that, once this enzyme acts on the degradation of arginine, this would result in the formation of ornithine that would enter the urea cycle to remake arginine endogenously.[69, 70]

The use of arginase had already been suggested in 1974 in a study in rabbits with ocular herpes where there was an accumulation of arginine in the tear ensuring the multiplication of the herpes hominis virus. The main source of arginine was the squamous epithelium of the infected cornea and, with its abrasion, it was found that the arginine content in the tear was reduced to equal the content in the tear of healthy rabbits. A low content of arginase in the tears of rabbits affected by ocular herpes was

also observed, suggesting that to reduce the local arginine produced by the squamous epithelium affected by herpes, an eye drops could be supplemented by arginase, which would result in the control of the herpetic process.[85]

As several arginine-depleting enzymes, similar to arginase, have been shown to be safe and effective in reducing the levels of this amino acid and their use have been suggested in further clinical studies in COVID-19 patients, which once again reinforces the viral activity of arginine also in SARS-CoV-2.[70]

It is known that endogenous renal arginase can be stimulated by another amino acid, L-lysine, which would lead to an increase in arginine metabolism and consequently control of viral replication, [29, 30] and it could be a new line of research with the amino acid lysine.

3.2.2 – L- lysine: pharmacological aspects

L-lysine (Lys) is (S)-2,6, -diaminohexanoic acid, a product of hydrolytic cleavage of proteins by digestion. Boiling with hydrochloric acid, a chemical process, results in the formation of many lysine salt forms such as lysine L-dihydrochloride, L-lysine monohydrochloride, calcium lysinate, lysortin (L-lysine mono-orthoate), succinate of L-lysine, lysine clonixinate and lysine acetylsalicylate [66] however, as supplements is commonly sold in capsules or tablets in lysine hydrochloride formulation since 1955, being isolated for the first time from casein (milk protein), in 1889 by the German dentist Heinrich Drechsel.[29]

Its hydropathy index < 0 characterizes it as polar (hydrophilic) and because it has a pKa of 10.53 in the side chain (R) and a second amine group in the R, at neutral pH, becomes a protonated basic amino acid, i.e., cationic [66] which characterizes this amino acid as a chelator for some metals.[86]

Classified as an essential amino acid not produced by the body, it must be acquired primarily through adequate food intake with a balanced inclusion of meats, dairy products and grains. The ideal minimum concentration of lysine for adults can be acquired with the daily intake of protein, however, there are many foods with a lower lysine concentration than this minimum value, indicating the increased amount of protein consumption in these cases.[87]

The values in grams/day of L-lysine through food were estimated, by some authors, between 4 and 5 g/day in adults with adequate diets [88, 89] however, the daily

requirement in a 70 kg adult, would be between 800 and 3,000 mg [30] and in face of supplementation necessity, the dose of 3g/day is safe without having adverse effects.[87, 90]

Other doses, between 500 and 7,500 mg/day, were tested in a group of subjects with reports of headache and gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhea approximately 6 h after doses of 7,500 mg. The limit dose/day would be approximately 6,000 mg, but the safest doses would be between 500 and 3,000 mg/day.[90] Chronic use was also discouraged.[27, 90, 91]

If theoretically around 4-5 g/day of lysine is ingested through food, a supplementation with 3g (loading doses) would be safe in the face of a viral outbreak, as it would not be much higher than the values (7,500 mg) that caused discomfort, according to the study of Hayamizu and col in 2020.[90]

Routes of administration

The oral route is preferred, although lysine supplements can be injected intravenously or intramuscularly.[29, 86] There is still no consensus regarding oral route in fasting condition[27, 92, 93] or with food.[29, 94]

What has already been suggested is that taking it with or separately from meals is a variable that needs to be investigated as the pharmacokinetics of lysine may differ between these two modes of administration. The free lysine when supplemented with meals compared to the free amount when taken between meals also deserves attention because of the movement of free lysine in and out of muscle storage.[29]

Toxicology

It is known that in patients with heart disease, there must be caution in prescribing lysine concomitantly with calcium supplements, as there may be an increase in the absorption of this mineral by the intestine as well as a reduction in its elimination by the kidneys, which would be harmful for these patients.[95]

Patients with sexual impotence, gallstones, asthma or immune dysfunction should also be monitored more closely if they need to be supplemented with this amino acid and chronic use should always be avoided [91] as well as in patients with human immunodeficiency virus (HIV). Studies suggest that lysine can increase the viral load in these patients, depending on the HIV lineage, as well as the high consumption of proteins rich in this amino acid in these patients.[74, 96, 97]

Lysine supplementation is absolutely contraindicated in patients with hyperlysinemia/hyperlysinuria, congenital metabolic disorders in neonates [72, 73] as well as in those with hepatic and/or renal failure.[29, 86]

Another important fact is that there may be increased toxicity of aminoglycosides if they were ingested by patients receiving lysine,[95] but most available reports concerning lysine toxicity, have been well reviewed demonstrating its safety as a dietary supplement at recommended doses.[29]

Absorption

The absorption rate of lysine added to wheat gluten is similar to the absorption rate during protein digestion, showing that lysine supplements are absorbed at fully effective rates in correcting their shortage in the diet.[29, 87]

During their absorption, six transport systems for amino acids across the cell membrane were identified, only two of which are exclusive to basic amino acids such as lysine. These same systems are also used by arginine [29] which reinforces the competition between these amino acids.

Absorption begins in the lumen of the small intestine, more specifically in the brush border region of enterocytes through active sodium-dependent transport. It is also absorbed in the paracellular region of the intestinal mucosa, but passively. Once absorbed, it will be used by the enterocytes themselves in their functions and the excess will be sent to the bloodstream, more specifically to the hepatic portal circulation. The transport of lysine by enterocytes to the splanchnic circulation occurs through the basement membrane region, passively through hydrophilic channels or also through the paracellular region.[66, 67]

Distribution

When it leaves the enterocytes in its free form, it will be distributed by the splanchnic circulation to the liver where it will be partially metabolized, used by hepatocytes in their functions or be involved in new protein synthesis. Unmetabolized lysine, not used by hepatocytes or resulting from hepatic protein metabolism, will be rapidly transported to other tissues where it can be metabolized or used for cellular functions. In muscle tissue, there will be a high concentration of lysine after 5-7h of ingestion, creating a temporary reservoir that will supply nutritional deficiencies, however, in this tissue it will not be metabolized.[29, 98]

Metabolism

Lysine can be metabolized in various tissues, but mainly in the liver and brain.[72] Its first-pass splanchnic oxidative catabolism is around 30%, suggesting that a good part of the amino acid was used for protein synthesis and part went into the circulation. The first step in the main pathway of lysine catabolism (saccharopine pathway) is its condensation with ketoglutarate to form saccharopine which, converted by saccharopine dehydrogenase, will form an α-aminoadipic semialdehyde and glutamate. Oxidation and decarboxylation of semialdehyde lead to the formation of carbon dioxide and acetyl-coenzyme-A as final products. There is evidence of an alternative pathway for L-lysine catabolism involving pipecolic acid as an intermediate product, but it appears to be of minor importance in normal human metabolism.[87, 98] However, later studies have detailed that both routes are used depending on some factors. In mitochondria the saccharopine pathway is used with the formation of acetyl Co-A + CO2 and in peroxisomes the pipecolate pathway resulting in the semialdehyde α-aminoadipate and later acetyl Co-A + CO2. In the infant brain and in most tissues, the most commonly used pathway for oxidative catabolism is the saccharopine pathway, while in the adult brain the predominant pathway is the pipecolate pathway.[99]

Excretion

Lysine in its free form can be excreted in the face of rare metabolic changes with lysinuria and cystinuria that must be controlled due to the risk of death, especially in neonates [72, 73] but, only excess lysine in healthy people is metabolized, i.e., excess amino acids are degraded, leaving the respective carbon chains and the amino group, which is converted into metabolites and these will be excreted.[73]

Once bound to a cell, lysine will develop its functions such as participating in carbohydrate metabolism helping to produce energy by converting it to acetyl CoA a precursor of another amino acid, L-carnitine, its ketogenic action is suggested because L-carnitine uses fatty acids for energy production in mitochondria. L-lysine helps in the biosynthesis of collagen and elastin as well as increases the absorption of calcium by the intestine, being recommended for the treatment of osteoporosis.[87]

Metabolic, therapeutic and viral activities.

Considered extremely necessary for the formation of all the body's proteins,

lysine plays an important role in the production of hormones, enzymes, antibodies, calcium absorption, muscle formation as well as their recovery from sports injuries.[93]

In addition to these functions, it participates in processes that have great clinical significance in the treatment of viral infections,[21, 25-27, 77, 91] anxiety, migraine, mood disorders, Alzheimer's, alopecia and some cardiovascular diseases.[93]

Its antiviral capacity in the treatment of herpes simplex, indirectly, results in lower risks of neurodegenerative damage and consequently in protection against Alzheimer's disease.[100] This relationship of HHV-1 with Alzheimer's makes lysine a doubly protective amino acid by preventing viral relapses and consequently neurodegenerative disease.

Being considered the amino acid with the highest concentration in the proteins that make up neurons, it also exerts a modulatory action on neurocellular proliferation, differentiation and excitability. It acts on the function of neurotransmitters by developing an anxiolytic action by increasing the affinity of the GABA-benzodiazepine-receptor complex. Animal studies suggest an increase in pain threshold when using lysine.[101]

By participating in collagen synthesis and antibody production, it promotes accelerated tissue repair and infection control. Studies have shown a positive action of this amino acid in reducing the healing time of lesions caused by herpesviruses (HHV-1 and HHV-6\7), the number of lesions (HHV6/7) and the severity of lesions (HHV-1 and HHV- 6\7). Regarding HHV-1 recurrences, there was an increased interval between outbreaks with an annual reduction of recurrence episodes as well as an action in the control of the clinical evolution of lesions, often inhibiting the development of initial lesions (HHV-1).[21, 25-27]

As known, arginine will convert into nitric oxide and NO can be toxic depending on concentration for cells, a “double-edged sword” [71] and in this concept, arginine as a precursor of NO, could have in some situation a negative effect by damaging the tissues, indirectly.

In pancreatic injuries induced by the chronic use of L-arginine, L-lysine can attenuate the damage to the pancreatic tissue by also inhibiting the release of the inflammatory cytokine IL-6 and increasing the antioxidant activity.[102]

The antagonism of lysine with arginine by competition has been discussed [30, 103, 104] since during absorption in the intestine or during transport across cell membranes, both compete for the same receptors. In the renal tubules, lysine further induces arginase

production, resulting in the degradation of arginine to metabolites. [29, 30, 73, 98, 103]

This mechanism on arginase, refers to studies where enzymes, that degrade arginine, were tested to control the arginine viral action.[70, 84, 85]

All these actions of lysine on an amino acid with viral activity (arginine), give it an "indirect" antiviral action.

The first studies with lysine competing with arginine date back to the 1960s. Herpes simplex viruses were cultured and placed in test tubes with culture medium enriched with 13 amino acids. Subsequently, the viral expression in the culture medium with an amino acid deficiency was analyzed. In the tube where the lysine was removed, there was an increased viral expression while in the one where the arginine was removed, the viral units went into latency with lower expression. When assays were performed using culture media with only these two amino acids, it was found that in the units with lysine and without arginine, the viruses went into latency and when lysine was suppressed with the addition of arginine, the viral expression was greatly increased. As higher doses of lysine were inserted, fewer plaque forming units (PFU) were counted, however, there was a limit. If the amount of lysine was increased, viral expression increased again.[23]

This can be explained by the fact that these two amino acids compete for the same carriers [67, 73] as well as the fact that the cell, when saturated by the high bioavailability of free lysine, would inhibit its absorption,[67] reinforcing the non-need for chronic protocols with high doses of lysine.

Several others in vitro studies [24, 75-77, 81] and others in vivo [21, 25-27, 91, 94] were performed with lysine.

A double-blind multicenter study with a placebo group and a group treated with oral L-lysine monohydrochloride (1g 3x/day for 6 months) in the prevention and treatment of recurrent herpes simplex infections showed that in 74% of the treatment group and in 28% in the placebo group, symptoms were milder in lesions that appeared after the start of treatment. There was also a greater reduction in recurrences in the lysine group versus placebo ($P < 0.01$). Healing time was significantly shorter in the treated group ($p<0.05$) showing the efficacy of L-lysine.[105]

Other doses of L-lysine were also tested in 41 patients in a double-blind crossover study. The group was divided into patients who received 624 mg/day for 24 weeks and then another 24 weeks with placebo with dietary arginine suppression, while the others received 1,248 mg/day following the same schedule including. Patients in the

1,248 mg /day group reported a significant reduction in recurrent HSV-1 outbreaks during supplementation, however, the 624 mg group showed no significant difference between the two time points (placebo and treated).[106]

Another prospective, paired study was performed on a group of 12 individuals with recurrent herpes labialis lesions. Patients who were using only topical antiviral therapy and with manifestations ranging from one or more episodes/month to one episode every 3 months, i.e., 4 or more episodes/year, were included. All reported the complete evolution of the lesions (prodromic, clinically active and reparatory) with an average cycle of 7 to 10 days. The protocol with lysine hydrochloride 500 mg/day fasting was maintained for 30 days with dietary arginine suppression. After this period, they were instructed to maintain the lysine/arginine balance for another 11 months, avoiding foods with a high concentration of arginine. Comparing the 12 months of therapy with the previous 12 months, there was an average reduction of 49% in lesion repair time and a 63% average reduction in the number of annual recurrences.[107] These same patients were followed for 8 years, with the protocol of 500 mg/day of lysine hydrochloride for 30 days every 12 months, maintaining control of the lysine/arginine balance in the diet. A significant year-to-year effect was observed in reducing the annual incidence of recurrent herpes. Faced with the imminence of a viral outbreak (prodromic phase), they immediately used 3g single dose of lysine, which resulted in lesion involution within 24 hours, but even so, they were considered as recurrence during the study.[25]

A rare case in the literature of herpes simplex reactivation in the palate and lip after each dose (2) of the AZD 1222 vaccine was also controlled with the use of 3 grams of lysine, a loading dose in the prodromal phase, causing the manifestation to be suppressed in the first hours after therapy.[27]

For successful of viral multiplication control, treatment with L-lysine must be instituted at the beginning of the manifestations, in the prodromal phase, with loading doses in order to compete with arginine, an important amino acid for initial viral replication.[25, 27, 75, 76] The same is recommended with the use of allopathic antivirals.[60] This protocol prevents many lesions from progressing to the clinical phase, disappearing even in the prodromal phase or at the first clinical symptoms.[25, 27]

Lysine has also been studied as an additional component to antivirals, such as penciclovir, an antiviral for herpes simplex, with the hypothesis that it could potentiate antiviral effects without pharmacological damage. The planning of new formulations

and the development of new strategies would be important in the war against viral diseases and association of drugs with the amino acid could be an alternative.[108]

In 2020, a group of researchers suggested that new clinical trials be developed to better understand the potential role of lysine in patients with eye infections with HSV, another comorbidity caused by the virus with devastating effects on the cornea. There are nearly 500,000 cases of active herpes simplex eye each year in the United States. Recurrent manifestations can lead to scarring and thinning of the cornea. During flare-ups, the patient has a corneal ulcer called a dendritic ulcer that causes pain, photophobia and tearing, and recurrence can lead to blindness. Corneal transplantation becomes risky as the virus can damage the new cornea, which leads to an interest from clinicians in therapies that reduce the frequency of viral recurrence.[109]

Patients with ocular herpes are treated with acyclovir, but this may have an impaired effect in those who take concomitant use of arginine supplements.[19, 20] The use of lysine together with acyclovir in the treatment of keratitis may have beneficial results by competing with endogenous or exogenous arginine, but in this case, arginine control should also be considered.

With the vast literature on this amino acid in the control of herpes simplex, researchers have linked its use to the possible control of another herpesvirus (HHV-6/7). HHV-1 can be controlled by acyclovir and lysine, HHV-6/7 controlled by acyclovir could then be controlled by lysine being prescribed in two cases of pityriasis rosea (PR) in carriers of latent HHV-6/7 possibly reactivated, one for insect bites and the other for vaccine. The protocols were designed according to the age of each patient and started on the 14th day of the appearance of the medallion and with the appearance of daughter lesions, an advisable deadline for intervening at the beginning of viral multiplication. The amino acid therapy was maintained for 30 days, showing a reduction in the disease cycle, in the number and severity of lesions.[21, 26]

Recently, lysine supplementation and concomitant reduction of intake of arginine-rich foods have been suggested as prophylactic and therapeutic regimens against SARS-CoV-2 and Influenza A (H1N1) virus. The authors showed that lysine and its ester derivative could efficiently block infection by SARS-CoV-2 and H1N1 (RNA virus with multiplication in the endosomes of the host cytoplasm), while arginine and its ester derivative significantly increased the infection. It was concluded that these basic amino acids do not interfere with the fusion of the spike protein with the angiotensin-converting enzyme 2 (ACE2) receptor, nor do they interfere with

endocytosis however, in the first 6 hours post-infection, the balance of these amino acids can prevent viral replication in the cytoplasm (Virus RNA) possibly by interfering with the endosomal acidification necessary for the replication of these viruses in this organelle.[77]

Another study does not conclude like the previous study as it infers that arginine residues in the spike protein may be crucial for stabilizing the viral interaction with ACE2 facilitating viral entry.[110]

A study with other coronaviruses concluded that in a low arginine environment the production of nucleocapsid proteins would be impaired since they have 6.9% arginine.[111] A defective nucleocapsid can result in naked virus particles.[24, 76]

In view of these studies, it can be thought that arginine depletion, due to a reduced intake of foods rich in this amino acid, such as lysine antagonism, could impact several stages of the SARS-CoV-2 viral cycle. Agreeing with Melano and col [77], while more studies are not developed, the arginine/lysine balance must be observed in the midst of the COVID-19 pandemic.

It has already been discussed that viruses accounted for about 60% of human infections with great concern for the public health and socio-economic system, causing infections with a high rate of morbidity and mortality in the world population [112] and that the emergence of viruses resistant to the available drugs added to the limitation of alternative antiviral therapeutic measures, the search for new antiviral molecules and the development of therapies with fewer side effects was necessary.[112, 113] A few years have passed but this scenario, in the face of the current pandemic, remains the same.

To avoid reactivation of latent viruses, it is important to control triggers and maintain a lysine/arginine balance in the diet. Patients with multiple relapse episodes can still supplement L-lysine for a limited time as prophylactic therapy.[25, 107]

To control the multiplication of some viruses, when active, an increase in the supply of L-lysine by supplementation with reduced arginine intake is indicated.[21, 25-27, 77]

Dosage

The optimal dosage of L-lysine for prophylaxis against relapsing herpes simplex is not yet well-defined, with doses ranging between 500 and 3,000 mg daily. A reasonable recommendation would be between 500 and 1,000 mg/day for limited time prophylaxis, reserving higher doses of 3,000 mg/day for active outbreaks for a limited time.[25, 27, 91]

Our protocol for the control of herpes simplex, since 1994, is for a limited time, it is 500 mg/day to 1g/day for 30 days, depending on food control and body weight, both for the control of relapses and for the treatment of lesions. However, we prescribe 3g as a single loading dose at the first signs of an infection or reinfection, always in fasting.[25, 27, 107] In all these years we were not aware of any adverse effects in our patients and several of them were followed up for at least 8 years.[25]

The protocol for PR also included a single loading dose of 3g (within up to 14 days) and doses of 500 mg/day for 30 days in adults.[21] In the case of the child, the doses were 250 mg/day without a loading dose, which proved to be safe and effective.[26]

Researchers report that in children, safe doses administered for food supplementation vary widely, ranging from 53 mg/day to 459 mg/day at ages ranging from 2 to 10 years [90] but the dose of 250 mg/day was the most used, being administered to 211 children aged 5-15 years for 9 months without any complications.[114]

The available evidence on the safety of long-term and/or high-dose lysine supplementation for the general population is inconclusive. Doses of 3,000 mg or more should not be recommended in the long-term as there is a chance of kidney damage. It should not be recommended for people with relative arginine deficiency. People suffering from asthma, sickle cell anemia, kidney disease or small bowel complications should be under proper medical advice. Also, caution is needed regarding men with reproductive health issues such as low sperm count or erectile dysfunction, as well as people with hypercalcemia, gallbladder disease, cardiovascular disease, pregnancy, and breastfeeding.[95, 115]

4 – CONCLUSION

Antiviral therapies are not yet able to interfere with a latent virus, however, at the initial moment of an infection or viral reactivation, they may be able to interfere with the virus adhesion and fusion and/or in viral proteins formation that play important roles in infection control.

The amino acid lysine may contribute to the inhibition of some of these phases by antagonizing arginine, an essential amino acid for some viruses. Lysine also promotes an increase renal arginase, catabolizing arginine. The control of reactivation

triggers such as the imbalance of the lysine/arginine balance in the diet is important, as is a greater supply of L-lysine, in the diet or by supplementation, in the face of some infections.

Although there is evidence on the importance of these amino acids in viral control, more studies are needed, aiming at new antiviral therapies with fewer side effects.

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Maria Cristina Pedrazini - researcher responsible for choice of theme, design of the article, bibliographic review and writing.
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TABLES

Table 1 – Herpesviridae Family
Source: Adapted from Rechenchoski et al., 2016; Grind, 2013.

Table 2 - Arginine/Lysine ratio in food proteins
Source: Adapted from Flodim, 1997; Gaby, 2006

Table 3: Pharmacological information of L-lysine and L-arginine
Source: Adapted from Nelson DL & Cox MM, 2017

Table 1 – Herpesviridae Family

Disease	Virus	Subfamily	Oral Manifestation	Other manifestations	Target Cell	Latency
Herpes Simplex virus 1 (HSV1)	HHV-1	Alpha	Ulcers	Ocular keratitis, encephalitis, meningitis	Muco-Epithelial	Sensory ganglion and cranial nerves
Herpes Simplex virus 2 (HSV2)	HHV-2	Alpha	Ulcers	Genital ulcers such as HHV-1	Muco-Epithelial	Sensory ganglion and cranial nerves
Varicella-zoster virus (VZV)	HHV-3	Alpha	Possibility of ulcers	Chickenpox, Herpes Zoster	Muco-Epithelial	Sensory ganglion and cranial nerves
Epstein-barr virus (EBV)	HHV-4	Gamma	Leukoplakia, periodontitis, nasopharyngeal carcinoma	Mononucleosis, lymphoma	Epithelial, B cells	Memory B cells
Cytomegalovirus (CMV)	HHV-5	Beta	Periodontitis	Mononucleosis	Epithelial, monocytes, lymphocytes	Monocytes and lymphocytes
Roseola Virus	HHV-6	Beta	-	Roseola Infantum	Monocytes, macrophages, T cell	Monocytes, macrophages, T cell
Roseola Virus	HHV-7	Beta	-	Roseola Infantum	Monocytes, macrophages, T cell	Monocytes, macrophages, T cell
Oncovirus (e.g. KSHV)	HHV-8	Gamma	-	Kaposi's sarcoma, non-Hodgkin's lymphoma	Lymphocytes, epithelial	B cells

Note: Adapted from Rechenchoski et al., 2016; Grinde, 2013.

Table 2 – Arginine/Lysine ratio in food proteins

Food	Amount	Ratio of arg/lys	Amount of lysine (mg)	Amount of arginine (mg)
Low arginine to lysine ratio				
Chicken	85 g	0,71	2232	1584
Salmon	85 g	0,65	2014	1309
Liver, beef	85 g	0,82	1671	1363
Pork	85 g	0,93	1586	1470
Cheese	85 g	0,36	1650	600
Balanced arginine to lysine ratio				
Oatmeal flakes	90 g	1	600	600
Medium Egg (no shell)	51 g	1	400	400
High arginine to lysine ratio				
Wheat flour	100 g	1,7	248	422
Chocolate	100 g	2	2000	4000
Granola	100 g	1,85	500	925
Cashews	21 g	2,6	185	481
Peanuts	100 g	3,15	1036	3269
Almonds	16 g	4,7	145	683

Note: Adapted from Griffith *et al.*, 1978; Flodin, 1997; Gaby, 2006

- HowMany.wiki: https://www.howmany.wiki/vw/--1--cup--of--uncooked-oats--in--gram

Table 3 – L-Lysine and L-arginine - pharmacological information.

Amino acid	Abbreviation/ Symbol	pKa values			pI *	Hydropathy index	Occurrence in proteins (%) **
		pK_1 (-COOH)	pK_2 (-NH3+)	pK_3 (R group)			
Lysine	Lys/K	2,18	8,95	10,53	9,74	(-) 3,9	5,9
Arginine	Arg/R	2,17	9,04	12,48	10,76	(-) 4,5	5,1

* Isoelectric point - is defined as the pH at which the amino acid has an equal charge (0)
** Average occurrence in more than 1150 proteins
Note: Adapted from Nelson & Cox, 2017.

FIGURE LEGENDS

Figure 1: Multiplication site in the cytoplasm - RNA Virus

Figure 2: Multiplication site in the nucleus - DNA Virus / DNA virus entry and exit steps.

Figure 3: Herpesvirus structures

Figure 4: Portal Vertex

Figure 5: Foods high in arginine

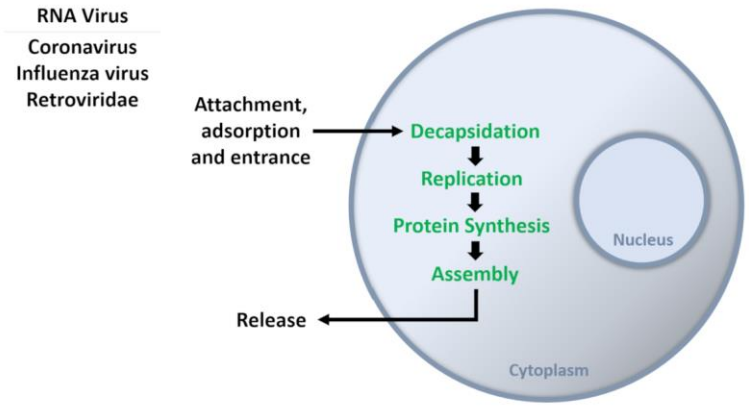

Fig.1 RNA VIRUS

276x152mm (300 x 300 DPI)

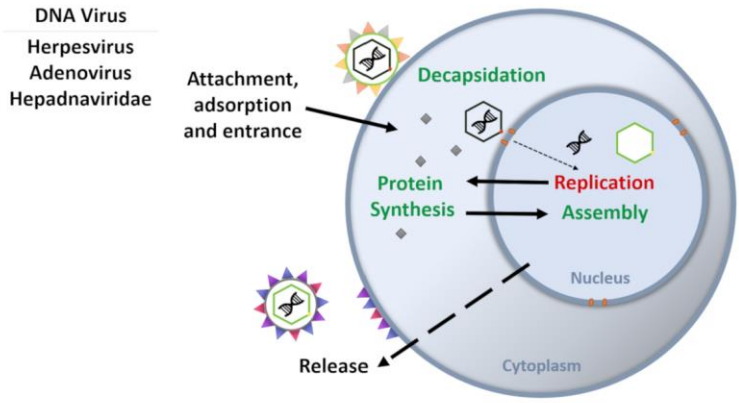

Fig. 2 DNA VIRUS

279x152mm (300 x 300 DPI)

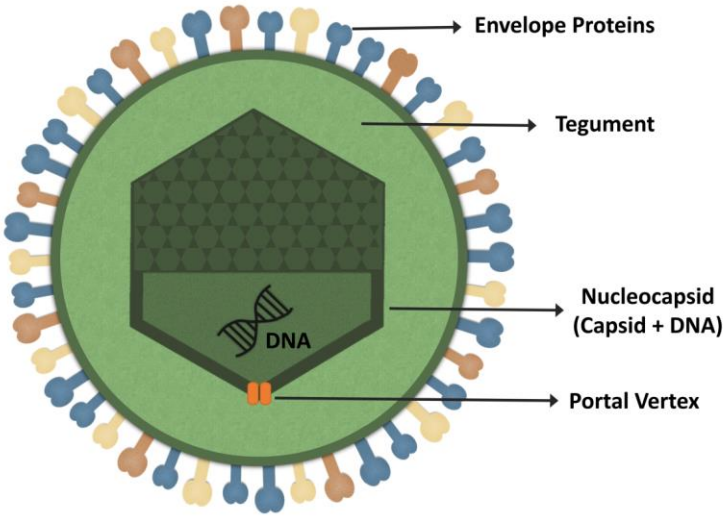

Fig. 3 HERPESVIRUS

291x206mm (300 x 300 DPI)

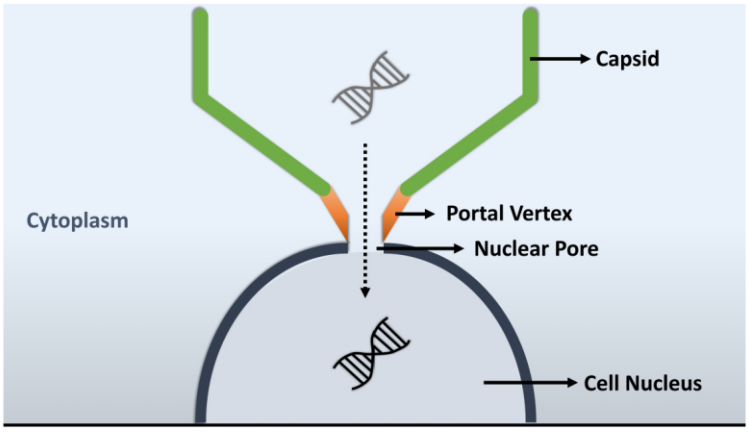

Fig. 4 Portal Vertex

306x175mm (300 x 300 DPI)

Fig. 5 High arginine foods

258x152mm (300 x 300 DPI)

3 DISCUSSÃO

3.1 Herpesvírus

Herpesvírus, vírus DNA envelopado, com latência vitalícia como sua principal característica (Gatherer et al., 2021), gera muita preocupação por ser praticamente pandêmico. Quase todo cidadão adulto já pode estar carregando um dos 8 vírus da família sem saber e, em algum momento, poderá ser reativado. Muitas infecções são assintomáticas e após uma primeira infecção, esses vírus entram em latência não podendo ser eliminados por antivirais. Quando reativados, por diversos fatores, promoverão um comprometimento sistêmico e agravos à saúde de alguns (Cohrs e Gilden, 2001; Luna e Silva, 2013).

A infecção viral herpética pode ser tratada por vários agentes antivirais com efeitos inibitórios podendo interferir ou na adsorção, ou na inibição da penetração viral nas células hospedeiras, ou na inibição da biossíntese de proteínas e DNA ou ainda interferir na liberação viral. Também tem sido aplicada terapias imunomoduladoras que estimulam o sistema imunológico do hospedeiro induzindo a autofagia para se eliminar o vírus. Medicamentos de amplo espectro visam atingir várias fases da multiplicação viral, inibindo a DNA polimerase, transcriptase reversa e neuraminidase, importantes enzimas no ciclo viral (Teuton e Brandt, 2007).

As drogas terapêuticas mais utilizadas na prática clínica são mesmo os análogos de nucleosídeos (inibidores da DNA polimerase) que afetam o processo de síntese de DNA impedindo o prolongamento de sua fita. São altamente eficazes contra a replicação ativa de vírus, ou seja, durante a multiplicação, nos estágios iniciais pós infecção. No entanto, em pacientes imunocomprometidos, o tratamento prolongado com esses medicamentos tem maior probabilidade para desenvolver cepas resistentes a eles devido às mutações da timidina nucleosídeo quinase ou DNA polimerase (Andrei e Snoech, 2021) o que nos leva a buscar novas terapias, como por exemplo o uso de aminoácidos.

O aciclovir é um dos antivirais mais prescritos para o tratamento das manifestações de herpesvírus (Pedrazini et al., 2018, Rodriguez-Zuniga et al., 2018; Chang et al., 2019; LoBue et al., 2019; 2020) sendo considerado padrão ouro (Stoopler et al., 2003; Santosh e Muddana, 2020) mas sabe-se que seu uso prolongado irá promover uma resistência viral devido à alteração na timidina quinase (TK) viral, o que impede a ação do aciclovir (Siakallis et al., 2009).

Recentemente, algumas vacinas vivas atenuadas foram disponibilizadas para aumentar a imunidade mediada por células reduzindo a incidência de recorrência de varicela-

zoster mas efeitos colaterais raros, são cada vez mais descritos devido ao aumento da administração destas vacinas em todo o mundo (Andrei e Snoech, 2021). Até o momento, nenhuma vacina eficaz contra o herpesvírus foi encontrada para erradicar completamente a infecção viral. As reativações continuam a ocorrer mostrando que o desenvolvimento de novos agentes antivirais alternativos, com efeitos colaterais mínimos e toxicidade reduzida, desempenha um papel significativo no direcionamento de diferentes mecanismos (Ruchawapol et al., 2021).

O conhecimento das características do hospedeiro, como por exemplo as nutricionais, pode favorecer a não perpetuação desses agentes infecciosos (Stephens et al., 2009) e diante dos estudos com os aminoácidos presentes na alimentação, chegou-se a conclusão que alimentos ricos em lisina poderiam favorecer o controle viral juntamente com um aporte reduzido do aminoácido arginina na alimentação (Pedrazini et al., 2007; 2018; 2021; Melano et al., 2021).

Um estudo clínico prospectivo pareado foi realizado em um grupo de 12 indivíduos portadores de lesões recorrentes de herpes simples labial. Foram incluídos pacientes que faziam apenas uso de terapia tópica com antiviral e com manifestações que variavam de um ou mais episódios/mês até um episódio a cada 3 meses, ou seja, 4 ou mais episódios/ano. Todos relataram a evolução completa das lesões (prodrômica, clínica ativa e reparatória) com ciclo em média de 7 à 10 dias. O protocolo com cloridrato de lisina 500mg/dia foi indicado em jejum, com um copo de água, sendo mantido por 30 dias com supressão de arginina alimentar. Após esse período, foram orientados a manter, por mais 11 meses, o balanço lisina/arginina evitando os alimentos com alta concentração de arginina. Comparando os 12 meses pós terapia com os 12 meses anteriores, verificou-se uma redução média de 49% no tempo de reparo das lesões e 63% de redução média no número de recidivas anuais (Pedrazini et al., 2007). Esses mesmos pacientes foram acompanhados por 8 anos com o protocolo de 500mg/dia de cloridrato de lisina por 30 dias/ano, a cada 12 meses, e sempre mantendo o controle do balanço lisina/arginina na alimentação. Foi observado ano a ano um efeito significativo na redução da incidência anual de herpes recorrentes. Diante da iminência de um surto viral (fase prodrômica), imediatamente faziam uso de 3g dose única de lisina, o que resultava na involução da lesão nas primeiras 24h mas, mesmo assim, foram consideradas como recorrência durante o estudo (Pedrazini et al., 2018).

Um novo artigo (Pedrazini et al., 2021) incluído no artigo 3, mostra um caso raro na literatura de reativação de herpes simples em palato e lábio após cada dose da vacina AZD 1222. Esta reativação também foi controlada com o uso de 3 gramas de lisina como dose de ataque na fase prodrômica, juntamente com supressão de arginina alimentar, fazendo com que a manifestação fosse suprimida nas primeiras horas após a terapia.

Os pacientes destes estudos faziam uso de aciclovir tópico em suas primeiras manifestações herpéticas resultando apenas na melhora do ardor e uma pequena melhora na cicatrização da feridas, que acabavam entrando na fase de reparação mais rapidamente do que quando não usavam. As reativações, o maior problema desses pacientes, não eram reduzidas com o uso do antiviral tópico e ao iniciaram o protocolo com o uso da lisina e supressão de arginina, além de perceberam uma redução na dor local, também perceberam que com a dose de ataque de 3 g de lisina, muitas lesões não evoluíam para a fase clínica ativa. Com a terapia preventiva apenas por 30 dias/ano e supressão de arginina na dieta, os números de manifestações anuais também diminuíram (Pedrazini et al.,2007; 2018), o que mostra a possibilidade antiviral deste aminoácido.

Outro estudo observou resultados semelhantes. De 26 pacientes avaliados em relação aos episódios anuais de herpes simples, 15 receberam 500 mg/dia de L-lisina por 6 meses enquanto o outros 11, receberam placebo. No segundo semestre, os pacientes que recebiam lisina receberam placebo e aqueles do grupo controle receberam lisina. Ambos os grupos fizeram supressão de arginina na dieta e ambos os grupos tiveram quedas no número de manifestações anuais. O grupo que recebeu lisina e supressão de arginina mostrou um maior redução dos episódios (Thein e Hurt, 1984), corroborando com os estudos de Pedrazini et al. (2007; 2018; 2021).

Tanto o HHV-1 como o HHV-2 coevoluíram com humanos por milhares de anos (Tognarelli et al., 2019) sendo considerados um dos patógenos mais frequentes adquiridos por humanos causando infecções endêmicas pois são transmitidos de pessoa a pessoa pelo contato nas lesões, com saliva, contato sexual, com o sangue ou pelo contato direto com utensílios utilizados pelo infectado. O primeiro contágio ocorre geralmente na infância e 90% das infecções são subclínicas. A manifestação clínica bucal mais frequente relacionada ao vírus do herpes tipo1 é a gengivoestomatite herpética que provoca febre, irritabilidade, dor ao deglutir, linfadenopatia regional e várias lesões ulceradas espalhadas na mucosa oral, lábio e nariz. No adolescente, a contaminação primária pode se manifestar apenas como uma dor de garganta ou

estar associada somente a um leve quadro gripal ou ainda, ser assintomática. A incubação apresenta curto período de 1 semana e como o vírus não é eliminado pelo sistema imunológico, após a manifestação clínica, subclínica ou assintomática, ele entra nos neurônios seguindo para os gânglios onde manterá o estado de latência. Quando reativados, podem provocar lesões com o aparecimento de bolhas aquosas em alguns locais como a pele oro labial, asa do nariz, língua, lábios, órgãos genitais, mucosa bucal e palato duro (Szczubiałka et al., 2016; Crimi et al., 2019).

As infecções podem ser benignas, porém o aumento na morbidade e mortalidade foi observado em neonatos e pacientes imunossuprimidos, incluindo pacientes transplantados e soropositivos para HIV (Espada et al., 2015), o que gera uma grande preocupação aos infectologistas.

Em 2016, os vírus HHV-1 e HHV-2 foram relatados como os principais responsáveis pela encefalite infecciosa, estimando entre 15.000 a 30.000 casos por ano no mundo com risco de letalidade de até 70% quando não tratados corretamente. A encefalite causada pelo HHV- 1 pode afetar principalmente crianças e adultos, enquanto a encefalite por HHV-2 geralmente está associada com neonatos (Quenelle et al., 2018). Podem ainda ser responsáveis pela cegueira (ceratite herpética não controlada). A capacidade de latência e reativação em indivíduos saudáveis é provavelmente dada pelos numerosos fatores de virulência que esses vírus desenvolveram para evitar as respostas antivirais do hospedeiro (Tognarelli et al., 2019).

O HHV-3 (VZV-Varicela Zoster) é um vírus preocupante, debilitante e durante a pandemia de COVID-19 tem sido reativado em uma frequência aumentada causando consequências aos pacientes com aumento da morbidade (Tartari et al., 2020; McMahon et al., 2021). Quando reativado, além do comprometimento dérmico também pode comprometer a mucosa ocular com sequelas em córnea. A úlcera dendrítica causada pela infecção herpética pode levar a cegueira (LoBue et al., 2019; 2020). Esse vírus também tem sido reativado pelas próprias vacinas anti SARS-CoV-2 (Bostan et al., 2021; Catalá et al., 2021).

Em imunocomprometidos internados em unidades de tratamento intensivo, as manifestações de HHV- 4/5 podem agravar o quadro respiratório devendo ser consideradas as terapias profiláticas (Niitsu et al., 2021). Uma taxa significativamente mais alta de detecção de marcadores ativos de infecção por EBV (HHV-4) em pacientes hospitalizados pela COVID-19 indica uma participação combinada de SARS-CoV-2 e EBV no desenvolvimento de pneumonia intersticial, o que gera maiores preocupações (Solomay et al., 2021).

O HHV-6/7 (Roseovírus) também vem chamando a atenção durante a pandemia da COVID-19 (Dursun e Temiz, 2020). Como discutido no primeiro e segundo artigos (Pedrazini e Groppo 2021; Pedrazini e Silva, 2021), o HHV-6/7 é o causador da sexta doença (*roseola infantun* ou exantema súbito), após um longo período de latência, pode ser reativado causando a pitiríase rósea (Chang et al., 2019; Daze e Dorton, 2020; Welsh et al., 2021; Veraldi e e Spigariolo, 2021). São doenças autolimitadas e auto resolutivas, porém, da mesma forma que outros herpesvírus, causam desconforto, constrangimento e em alguns pacientes, pode provocar o desenvolvimento de atopia. Durante a gravidez, nas primeiras 15 semanas de gestação, pode causar parto prematuro e morte fetal (Litchman et al., 2021). Em casos de prurido aumentado, o tratamento escolhido pelos dermatologistas envolve o uso de anti-histamínicos (Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021) e casos mais graves, a escolha se volta para o antiviral aciclovir (Castanedo-Cazares et al., 2003; Rodriguez-Zuniga et al., 2018) que é um dos medicamentos que inibe a replicação viral em até certos níveis, têm um espectro de ação restrito, não atua em vírus latentes, causa efeitos colaterais indesejáveis (Saxena et al., 2010) e o uso contínuo, pode promover resistência farmacológica assim como outros antivirais (Siakallis et al., 2009; Saxena et al., 2010).

Diante destes pontos negativos dos antivirais, a terapia com L-lisina também pode ser uma alternativa promissora para o controle da PR uma vez que pode agir nas etapas de multiplicação viral ao competir com o aminoácido arginina, um pró-vírus. Muito utilizada no tratamento do herpes simples, se mostrou uma possibilidade terapêutica, com menos efeitos adversos nas doses recomendadas, em mais esse vírus da família herpesviridae.

3.2 A L-lisina e o roseovírus – Pitiríase Rósea

Com a forte associação da PR com herpesvírus humano HHV-6/7 (Chang et al., 2019; Daze et al., 2020, Welsh et al., 2021; Pedrazini e Silva, 2021) terapias antivirais podem ser indicadas para controle da evolução da doença (Rodriguez-Zuniga et al., 2018, Contreras-Ruiz et al., 2019; Chang et al., 2019), assim como a terapia alternativa com aminoácidos L-lisina e L-arginina discutida nos artigos 1 e 2 (Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021), ambos mostrando resultados positivos e semelhantes na redução no tempo de cicatrização como limitando o número de lesões quando iniciados nas duas primeiras semanas, ainda na fase de multiplicação viral (Chang et al., 2019; Pedrazini e Silva, 2021).

Uma vez que a literatura é vasta sobre a importância do equilíbrio destes dois aminoácidos na replicação de vírus do herpes simples e, por ter mostrado resultados promissores em casos clínicos de herpes simples (Pedrazini et al., 2007; 2018; 2021), nos artigos 1 e 2 (Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021) foi proposto o tratamento com os aminoácidos no controle de reativações do roseovírus. A L-lisina foi prescrita em 2017 a uma criança com PR, portadora do vírus latente HHV-6/7 após um episódio de exantema súbito por volta dos 2 anos de idade. Aos 11 anos, após várias picadas de insetos, apresentou lesão primária (medalhão ou placa mãe) e secundárias (lesões filhas) com diagnóstico de PR. O ciclo seria de seis a oito semanas, em média. Com o surgimento de mais e mais lesões e aumento do prurido, uma solução de L-lisina (250mg/5ml/dia) foi prescrita por trinta dias, em jejum. Após o quarto dia da terapia, o ciclo de novas erupções foi interrompido, lesões iniciais regrediram havendo aceleração no reparo de lesões maiores iniciais, resultando na melhora do quadro (Pedrazini e Groppo, 2021).

O segundo caso foi em uma mulher de 53 anos de idade, fototipo II que apresentou uma lesão eritematosa em posterior de coxa direita após 14 dias da segunda dose da vacina (AZD1222) Oxford-AstraZeneca. Após 8 dias do medalhão inicial, novas lesões foram surgindo em panturrilha, nádegas e coxas. O diagnóstico foi de PR e a explicação seria o fator epidemiológico pois, um parente próximo com roséola infantum, ficou sob os cuidados da paciente possivelmente transmitindo por saliva o vírus HHV-6/7. O ciclo poderia ser de 6-8 semanas ou mais, devido a resposta imunológica exacerbada pós vacina. O tratamento consistiu no uso de L-lisina, 3 gramas dose de ataque e de 500 mg/dia em jejum por 30 dias, iniciando 14 dias após o medalhão. Após a 5ª semana pós medalhão, não houve novas erupções e o ciclo reparatório com lesões residuais seguiu até 8 semanas. A L-lisina colaborou para o controle da manifestação limitando o número de lesões e a localização, que ficou restrita às pernas e nádegas (Pedrazini e Silva, 2021).

Nos dois casos, os resultados são levemente distintos em relação à resposta à lisina, sendo a resposta mais lenta no adulto. Provavelmente, isso se deve às idades diferentes entre os pacientes, bem como a diferença no agente causador. Fica claro que uma reativação causada por picadas de insetos em uma criança, mostrou uma melhora mais imediata do que no adulto com um sistema imunológico ativo pelas vacinas recentes contra o SARS-CoV-2. Mesmo havendo a dose de ataque no adulto, a resposta foi diferente, levando mais de tempo para a

interrupção das novas manifestações dérmicas, como também um tempo maior de reparo. Porém, a melhora do quadro na percepção dos pacientes e nas análises dos médicos, foi nítida.

As doses foram traçadas de acordo com a idade, estudos prévios e com a anuência dos médicos envolvidos, sendo iniciadas no 14º dia do medalhão com o surgimento das lesões filhas, ou seja, ainda na fase ativa da doença. A pitiríase rósea, com sua lesão primária parecendo uma lesão fúngica isolada, de 7 a 14 dias, normalmente deixa dúvidas tanto nos pacientes como nos dermatologistas que a princípio recomendam cremes antifúngicos. Somente após o surgimento das lesões filhas, o diagnóstico é conclusivo. A terapia foi mantida por 30 dias mostrando redução no ciclo da doença, no número e na gravidade das lesões, promovendo conforto aos pacientes (Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021).

Um único estudo sobre o uso da lisina em PR foi publicado em um painel científico, por Roxo et al. em 2018. Neste estudo, dois pacientes adultos (25 e 26 anos) acometidos por PR receberam 500mg de L-lisina a cada 12h por 15 dias, iniciando o tratamento em fase avançada da doença (com evolução de 3 e 4 semanas, respectivamente). Após 21 dias de tratamento, houve remissão total da PR, ou seja, a cura ocorreu respectivamente 6 e 7 semanas após o início da PR, sendo incerto se a remissão seria causada pelo uso do aminoácido ou pela evolução média usual da doença. Já no artigo 1, Pedrazini e Groppo (2021) recomendam que o ideal seria iniciar o tratamento com L-lisina, para controlar a multiplicação viral, no início das manifestações. O mesmo ocorreu no caso descrito no artigo 2, Pedrazini e Silva (2021), onde além de iniciar a terapia com os aminoácidos na fase precoce das manifestações, foi prescrita uma dose inicial de ataque de 3 g para o adulto para que houvesse uma maior competição com a L-arginina circulante no plasma e tecidos.

O termo pitiríase rósea significa “escamas finas rosadas” (González et al., 2005) se apresentando como uma manifestação cutânea dermatológica diagnosticada pelas lesões eritêmato-pápulo-escamosa distribuída em tronco e extremidades. Em 1860, o médico francês Camille Melchior Gibert, identificou lesões que acometiam pessoas saudáveis, principalmente crianças e jovens entre 10 e 35 anos de idade (Parsons, 1986; Leung et al., 2021).

Foi classificada como uma doença de pele benigna e que poderia estar distribuída em tronco e extremidades. Na grande maioria das vezes o primeiro sintoma seria o surgimento da “placa mãe” ou “medalhão” ou “lesão primária”, uma lesão única, ovalada, rosada em tórax, membros inferiores ou abdome apresentando crescimento centrífugo chegando a medir de 2-10 cm de diâmetro. Essa lesão pode permanecer isolada e única por 1 ou 2 semanas, quando então

novas lesões “filhas” ou “secundárias” surgiriam. Essas lesões são menores, de 0,5 a 1,5cm, surgem em tórax, abdome, costas e proximais dos membros. A fase inicial se caracteriza por placas de cor salmão, na fase clínica uma descamação centrípeta se inicia e por fim, o processo de cicatrização é caracterizado pelo clareamento das manchas (Daze et al., 2020; Pedrazini e Groppo, 2021)

Aproximadamente apenas 5% dos casos clinicamente típicos de PR são precedidos por sintomas prodrômicos, incluindo dor de cabeça, desconforto gastrointestinal, febre, mal-estar e artralgias (Parsons, 1986; Leung et al., 2021).

Apesar de 75% dos casos acometerem pessoas de 10 a 35 anos, existem relatos de que em 25% dos casos de PR, a idade dos acometidos podem estar em outra faixa, de 3 meses a 10 anos e de 35 a 83 anos (González et al., 2005). Diversas manifestações atípicas da doença têm sido registradas como a presença da placa mãe sem sinais de lesões secundárias, presença de várias placas mães ou ainda a ausência desta placa (Chuh et al., 2007) sem excluir o diagnóstico de PR. A evolução da doença varia de 6 a 8 semanas podendo permanecer de 3 a 6 meses com alterações reversíveis na coloração da pele (Browning, 2009).

No artigo 2, Pedrazini e Silva (2021) apontam que geralmente a PR se apresenta como uma doença assintomática, auto-resolutiva e que não requer tratamento porém, em determinadas situações, fármacos como anti-histamínicos e corticóides tópicos auxiliam no prurido mas, neste caso, esse efeito foi alcançado com o protocolo de aminoácidos A automedicação deve ser evitada pois algumas substâncias podem provocar irritações e em quadros descamativos, com prurido acentuado ou manchas residuais persistentes, o dermatologista/infectologista/pediatra deve ser consultado.

O banho de sol também é indicado tanto para o prurido como para melhora das manchas brancas residuais, porém, os benefícios destes tratamentos são temas de discussões (Leung et al., 2021) pois existe a hipótese de que o banho de sol pode provocar um exantema aumentado da doença, ou seja, um efeito rebote (Castanedo-Cazares et al., 2003). No caso da roséola infantile, primo infecção do HHV-6/7, o banho de sol deve ser evitado tanto devido à febre próxima de 40^{o} C como devido ao aumento do exantema típico da doença que acomete crianças de 6 meses a 2 anos (Mullins e Krishnamurthy, 2021). Essa orientação foi indicada à criança do relato de caso de Pedrazini e Groppo (2021) e como a radiação solar também pode exacerbar a PR, fica ainda mais claro a possível associação da PR com a reativação do roseovírus, tema que por muito tempo gerou discussões.

Atualmente, essa é hipótese mais forte, a PR sendo causada pelos herpesvírus HHV-6/7 reativado (Leung et al., 2021; Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021; Veraldi e Spigariolo, 2021) por vários gatilhos e entre eles estão os fatores imunológicos em resposta a picadas de insetos (Pedrazini e Groppo, 2021) ou desencadeados por vacinas (Pedrazini e Silva, 2021).

Como todos os herpesvírus, o HHV-6/7 estabelece latência vitalícia onde a expressão do genoma viral é limitada, mas é distribuído às células filhas sem a produção de vírus infeccioso. A latência ocorre nos tecidos linfoide primário (medula e timo) e também secundários MALT (mucosa e pele). A célula-alvo proposta é o monócito (macrófagos quando em tecidos) mas foi também sugerido, como sítio de latência, as células progenitoras da medula óssea e células T (CD4+) como também os astrócitos, células do sistema nervoso central (Pantry e Medveczky, 2017). Uma vez latente pode ser reativado e sendo reativado deve ser controlada a replicação viral devido aos riscos de maiores comprometimentos como a meningite ou encefalites (Griffiths, 1997), as atopia (reações alérgicas genéticas despertadas pelo vírus), parto prematuro (Litchman et al., 2021) e a paralisia de Bell (Genizi et al., 2019).

3.3 Reativação Viral

A reativação é uma opção perigosa para o vírus pois durante uma replicação, a DNA polimerase, em DNA vírus, assume o comando da multiplicação da macromolécula viral. Vários outros mecanismos do hospedeiro serão ativados, inclusive seu sistema imunológico ou sua sinalização interna, levando a célula hospedeira à morte juntamente com o vírus. Algumas reativações não irão implicar em sintomas clínicos e isso é devido à resposta imune do hospedeiro como também do nível de produção viral, ou seja, da carga viral ativa (Grinde, 2013).

Curiosamente, o desbalanço de aminoácidos foi sugerido como um possível gatilho de uma reativação de vírus latentes (Tankersley, 1964; Becker et al., 1967) sendo preconizado que aminoácidos essenciais aos vírus fossem evitados e aqueles que interferissem na multiplicação viral, a suprimindo, fossem suplementados levando novamente o vírus a latência (Everitt et al., 1971, Griffith et al., 1981; Pedrazini et al., 2007; 2018; 2021).

A arginina está intimamente ligada à reativação de herpesvírus latentes que poderiam se manter em sua forma inativa devido a indisponibilidade deste aminoácido durante vários estágios do processo infeccioso pois na sua ausência, a síntese viral estaria prejudicada

e a formação de partículas virais completas, inibida. Quando disponibilizada, haveria uma reinfecção rápida e generalizada (Tankersley, 1964).

A reativação pode ocorrer devido ao estresse físico ou mental do hospedeiro, sendo considerados como estresse físico febre, exposição a raios ultravioletas e ao frio, picadas de insetos (Miranda et al., 2018; Pedrazini e Groppo, 2021), imunossupressão e a própria desregulação imunológica causada por alguns imunizantes (Mindell, 1986; Flodin, 1997; Sanchez et al., 2016; Simonnet et al., 2021, Pedrazini e Silva, 2021; Pedrazini et al., 2021).

O estresse psicológico, principalmente o crônico, é igualmente preocupante pois é geralmente imunossupressor e contribui, por meio da supressão das respostas imunes inata e adaptativa, para incapacidade de se controlar o vírus em estado latente levando a uma reinfecção viral com aumento da patogenicidade (Ashcraft e Bonneau, 2008).

Em meio a uma pandemia sem precedentes, os quadros de reativações virais aumentaram significantemente, podendo estar associados ao fato da COVID-19 ser uma ameaça exclusiva que contribui para o pânico e o estresse em massa, provocando transtornos obsessivo-compulsivos, estresse crônico e ansiedade, com resultados sistêmicos preocupantes (Shuja 2020).

As reativações também estão associadas a própria infecção viral da COVID-19 (Ehsani et al. 2020; Welsh et al., 2021; Veraldi e Spigariolo, 2021) explicando os casos de reativações de HHV-1/2 (Ardalan et al., 2021), HHV- 3 (Siddiqui e Hasnain, 2020) ou do HHV-6/7 (Welsh et al., 2021) em pacientes contaminados pelo SARS-CoV-2.

Os estímulos imunológicos provocado pelas vacinas anti SARS-CoV-2 foram apontados como gatilhos da reativação, por duas vezes, do herpesvírus HHV-1 (Pedrazini et al., 2021). O mesmo fator disparador, ou seja, a vacina AZD 1222 também foi apontado como causador da reativação de outros membros da família herpesviridae (HHV-6/7) no artigo 2, Pedrazini e Silva (2021). Os autores ressaltam, entretanto, que também outras vacinas para outros vírus promovem reativações, sendo importante não desencorajar o seguimento dos programas de vacinação.

Casos de herpes simples e herpes zóster surgiram como manifestação pós-vacinas anti-SARS-Cov-2 (UK Governement, 2021; Abdullah et al., 2021; Akdas et al., 2021; Fathy et al., 2022), mas estes vírus também foram reativados por outras vacinas, como a trivalente contra influenza, contra H1N1, anti hepatite A e contra a raiva (Ardalan et al., 2021).

A PR, por exemplo, também já foi reativada por vacinas contra varíola, tuberculose, gripe, papilomavírus, poliomielite, tétano, pneumococo, tríplice viral (difteria-coqueluche-tétano), hepatite B, febre amarela (Brzezinski e Chiriac, 2014) e H1N1 (Chen et al., 2011; Demirkan et al., 2019). A PR poderia, assim, surgir como uma reação secundária, menos específica, à resposta imunológica pós vacinas (Chen et al., 2011; Brzezinski e Chiriac, 2014; Papakostas et al., 2014; McMahon et al., 2021; Carballido Vázquez e Morgado, 2021; Abdullah et al., 2021; Marcantonio-Santa Cruz et al., 2021; Pedrazini e Silva, 2021).

Em um estado de imunidade alterada, a reativação do HHV-6/7 poderia resultar de uma reação orientada para a pele, mediada por células T (Papakostas et al., 2014; Ewer e Barrett, 2021) que inclusive é o local de latência dos roseovírus (Grinde, 2013; Rechenchoski et al., 2017).

As vacinas poderiam reativar vírus devido a falhas na resposta imune-inata ou mediada por células iniciadas pela vacinação (Siddiqui e Hasnain, 2020) ou a distração da resposta humoral devido à vacinação, poderia levar à perda do controle imunológico de vírus latentes (Richardson-May et al., 2021).

Como o balanço dos aminoácidos também foi citado como importante para evitar reativações (Tankersley, 1974; Pedrazini et al., 2007; 2018), mais estudos deveriam ser realizados com administração preventiva de suplementos de lisina com controle do aporte de arginina, previamente às vacinas em pacientes com vírus latentes, pelo menos naqueles sabidamente portadores de vírus latentes.

A lisina, além de uma atividade antiviral preventiva (Griffith et al., 1987; Pedrazini et al., 2021), também atua na resposta do sistema imunológico por participar da produção de anticorpos (Mindell, 1986; Singh et al., 2011) e poderia auxiliar, de alguma forma, na prevenção de reativações pelas vacinas. Isso é apenas uma hipótese a ser discutida.

Sabe-se que vírus em latência não sofrem a ação de antivirais, mas uma vez que ocorre uma reativação, o controle viral deve ser instituído com o intuito de se reduzir o número de partículas virais que voltarão para a latência e desta forma promover reativações futuras mais leves com menor dano aos tecidos (Napoletani et al., 2021). Estudos discutiram que evitar uma reativação de HHV-1, por exemplo, resultaria indiretamente em menores riscos de danos neurodegenerativos e consequentemente na proteção contra a doença de Alzheimer pois existe uma possível relação do HHV-1 com o Alzheimer (Rubey, 2010; Marcocci et al., 2020;

Napoletani et al., 2021). Isso faz da lisina um aminoácido duplamente protetivo ao impedir as recidivas virais e consequentemente a doença neurodegenerativa.

As reativações virais relatadas nos artigos 1, 2 e 3, tais como a pitiríase rósea, herpes zoster, herpes simples, vírus da família dos herpesvírus, podem ser tratadas com antivirais como o aciclovir (Das et al., 2015*;* Chang et al., 2016; LoBue et al., 2019; Schuierer et al., 2020; Bunz et al., 2020) mas a herpes simples e a pitiríase rósea também puderam ser controladas pelo protocolo com os aminoácidos (Pedrazini et al., 2007; 2018; 2021; Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021).

3.4 Aminoácidos: L-lisina x L-arginina

A lisina se enquadra no grupo de aminoácidos essenciais enquanto a arginina é considerada "semi-essencial" pois é sintetizada no organismo por meio da ornitina, mas como é totalmente consumida no ciclo da uréia, ela se torna indispensável na alimentação. São ambas consideradas proteinogênicas, ou seja, se encontram em todas as proteínas (Nelson e Cox in Lehninger, 2017), desta forma, o balanço na dieta acorre nas escolhas de alimentos, alguns mais ricos em arginina do que outros enquanto se tem aqueles mais ricos em lisina (Griffith et al., 1978; Flodin, 1997, Gaby, 2006).

O efeito do excesso de lisina nos níveis de arginina foi abordado em vários organismos, principalmente em aves, mostrando que em níveis normais de arginina, quando alimentados com uma dieta rica em lisina, havia um aumento dos níveis plasmáticos de lisina juntamente com uma redução de arginina em plasma e tecidos (Jones et al., 1967).

Vários estudos concluíram que suplementação de arginina na dieta reverte os sinais observados de excesso de lisina, corroborando a existência também de antagonismo arginina-lisina, porém esse antagonismo seria específico para cada espécie. O antagonismo arginina-lisina não foi bem estudado em humanos e pacientes com hiperlisinemia, devido a uma mutação em um gene que codifica uma proteína envolvida na quebra da lisina, não apresentavam níveis plasmáticos reduzidos de arginina, concluindo que nos humanos não haveria antagonismo entre esses aminoácidos (Bol e Bunnik, 2015). Porém, outros estudos mostraram evidências contrárias à essa teoria. A suplementação oral com arginina é a terapia mais recente em pacientes com erros inatos de metabolismo relacionados à lisina como a epilepsia dependente de piridoxina (PDE) e acidúria glutárica tipo 1 (GA1), devido justamente a esse antagonismo da arginina com a lisina (Bouchereau e Schiff, 2020; Schmidt et al., 2020).

O antagonismo por competição da lisina com a arginina tem sido discutido (Gaby, 2006), pois durante a absorção no intestino ou durante o transporte através das membranas celulares, ambas disputam os mesmos receptores (Griffith et al., 1981; Flodin, 1997; Gaby, 2006; L-lysine, 2007; Schmidt et al., 2020).

Nos túbulos renais, a lisina ainda induz a produção de arginase resultando na degradação de arginina em metabólitos e aumento da excreção destes (Griffith et al., 1981; Miller e Foulke, 1984; Flodin, 1997; Gaby, 2006; L-lysine, 2007; Bollenbach et al., 2019; Schmidt et al., 2020).

Importante citar que no terceiro artigo, de revisão, apresentado por Pedrazini *et al*, já foi discutido que alguns destes estudos descreveram a lisina como participante no aumento da produção de arginase nos túbulos renais e consequentemente, aumento da excreção de "arginina. Em seres humanos, a arginina não é excretada *in natura*, mas seus metabólitos são. Embora muitos estudos que tratem da excreção do aminoácido descrevam **"**aumento da excreção de arginina pela urina**"** (Griffith et al.,1981; Gaby, 2006; Bol e Bunnik, 2015), essa informação vem sendo transcrita de forma errônea pois partem de estudos em animais, os quais têm metabolismo de aminoácidos diferente dos seres humanos (Czarnecki et al., 1985). Foram também transcritas de um estudo em frangos, informando a excreção de uréia, ou seja, dos metabólitos da arginina e não do aminoácido (Austic e Nesheim, 1970), lembrando que aves excretam ácido úrico. Vários autores têm citado o estudo de Austic e Nesheim (1970) e referenciado como "excreção de arginina", fato inverídico e derivado da interpretação errônea do estudo. Particularmente em estudos realizados com aves, a lisina é citada como promotora do aumento de arginase e consequentemente excreção de arginina ou de uréia quando o correto seria excreção de ácido úrico. Essa forma errada de descrever o mecanismo de excreção da arginina, já foi corrigida no artigo 3 de Pedrazini *et al*, afim de interromper a perpetuação de um erro que vem se estendendo desde a década de 60.

Como a arginina está associada tanto à replicação como à virulência de muitos vírus (Tankersley, 1964; Gonczol et al., 1975; Wigand e Kumel, 1978), sendo inclusive essencial para a progressão e gravidade das infecções (Tankersley, 1964), essa ação sobre a arginase e a competição pelos mesmo receptores da arginina (Jones et al., 1967; Griffith et al., 1981; Flodin, 1997; Gaby, 2006; L-lysine, 2007; Schmidt et al., 2020), faz da lisina um aminoácido com ação antiviral "indireta".

A ação da lisina sobre a arginase promove a degradação de arginina. A arginase recombinante humana ou aquela removida de fígado de coelhos foram testadas no controle viral, devido à sua propriedade em degradar a arginina em ornitina e uréia (Kahán et al., 1979; Sanches, 2016; Grimes et al., 2021). Os resultados foram promissores, mostrando o quão é importante reduzir os níveis de arginina em organismos contaminados por vírus, inclusive o SARS-CoV-2 (Grimes et al.,2021).

Alguns estudos já foram conduzidos, usando a L-lisina juntamente com a supressão de arginina, na atual epidemia de SARS-CoV-2 e reforçam a importância da arginina neste vírus (Hoffman et al., 2020; Grimes et al., 2021; Melano et al., 2021), bem como a possibilidade da arginase recombinante humana como terapia anti SARS-CoV-2, pois a arginase (depletora de arginina) promoveria a não-replicação bem-sucedida do SARS-CoV-2 e, como este aminoácido é substrato para formação de NO, gatilho para a resposta inflamatória exacerbada do hospedeiro, a depleção da arginina poderia atenuar a infectividade e a resposta inflamatória grave do COVID-19. Sendo assim, o uso de enzimas semelhantes à arginase endógena seria uma potente alternativa terapêutica (Grimes et al., 2021).

Em relação aos herpesvírus, a literatura é vasta sobre a ação da L-lisina e L-arginina, principalmente no controle do herpes simples (Tankersley, 1964; Becker et al., 1967; McCune et al., 1984; Griffith et al., 1987, Pedrazini et al., 2007; 2018; 2021; Meira et al., 2019; Castro et al., 2019).

Mesmo que alguns autores discordem da ação antiviral da lisina ou do antagonismo entre os aminoácidos, criticando a grande maioria dos estudos *in vitro* e clínicos desenvolvidos (Bol e Bunnik, 2015), outros consideram uma boa alternativa de tratamento. A L-lisina poderia ser utilizada em pacientes queimados e portadores de HHV1/2 latente, o qual poderia ser reativado diante das queimaduras, agravando ainda mais o quadro clínico (Roberts et al., 2013). O controle da ceratite herpética também poderia ser beneficiado pelo uso do aminoácido (Moshirfar et al., 2020).

Embora a eficácia da lisina estaria mais ligada à prevenção do herpes labial e alguns estudos não corroborem com o uso da lisina para diminuir a gravidade ou a duração dos surtos (Tomblin e Lucas, 2001), a suplementação de lisina vem mostrando melhora na gravidade e na duração dos surtos de reativação de herpesvírus em pacientes acompanhados rotineiramente. A redução de arginina na alimentação também foi sugerida para potencializar a ação antiviral (Pedrazini et al., 2007; 2018; 2021), principalmente pela retirada da dieta do chocolate, rico

arginina (4%) e pobre em lisina (2%), e do amendoim (7,4% de arginina e 2.4% de lisina) (Griffith et al., 1978).

As conclusões antagônicas mostram a importância de mais estudos clínicos controlados com o uso da lisina e supressão de arginina em infecções virais. É importante também considerar que quando o consumo da arginina é equilibrado, o controle de ativações herpéticas é alcançado com antivirais alopáticos, como o aciclovir. Porém, se houver uma suplementação com arginina, nem mesmo esses antivirais seriam capazes de controlar a infecção. Nestes casos, os estudos foram conduzidos na ceratite herpética mostrando que com arginina, nem mesmo o aciclovir controlaria o herpesvírus (LoBue et al., 2019; 2020).

A arginina é absorvida no intestino delgado, metabolizada no fígado no ciclo da uréia e seus metabólitos, como a uréia, poderiam ser excretados pelo rim, enquanto a ornitina, citrulina e grupos aminos seriam reutilizados para o anabolismo de outras substâncias, inclusive de nova arginina. Esse aminoácido é obtido pela dieta ou produzido no citosol dos hepatócitos, enterócitos e células renais por meio da ornitina no ciclo completo ou parcial da uréia (Morris, 2016; Grimes et al., 2021).

A lisina também é absorvida no intestino através da membrana “borda de escova”. Uma vez absorvida, será utilizada pelos próprios enterócitos em suas funções e o excesso será encaminhado, através da membrana basolateral de forma passiva pelos canais hidrofílicos e região paracelular, para a corrente sanguínea mais especificamente para circulação porta hepática (Frenhani e Burini, 1999; Nelson e Cox, 2017). Essa disputa pelos mesmos carreadores trans-membrana explica a competição entre lisina e arginina durante a absorção celular muitas vezes favorecendo os vírus.

L-lisina e L-arginina por serem moléculas estruturalmente relacionadas, podem competir, durante a absorção no intestino, pelos mesmos carreadores, assim como durante o transporte pelas membranas celulares. Além disso, a célula pode se tornar saturada em um deles, diminuindo a velocidade de sua absorção deixando o outro livre para ser mais absorvido (Frenhani e Burini, 1999). Ainda, a depender do estado de uma célula, infectada por um vírus ou não, ela dará preferência pela absorção de um ou de outro (Kaplan et al., 1970). Essas informações são importantes para que se entenda a dinâmica lisina/arginina na possível atividade antiviral.

Em pessoas saudáveis, os níveis de lisina e arginina sérico podem variar de 82 a 249 e de 21 a 137 nmol/ml respectivamente (Stein e Moore, 1954; Thein e Hurt, 1984). O

excesso de lisina, nestas pessoas, não é excretado mas sim metabolizado, pois aminoácidos excedentes são degradados, restando as respectivas cadeias carbônicas e o grupo amino, que se ligará ao CO_2 sendo convertido em metabólitos a serem excretados (Schmidt et al., 2020).

Alguns vírus, como exemplo o HHV-1, durante sua produção de proteínas em uma célula hospedeira, absorvem do meio mais arginina do que lisina enquanto uma célula humana não infectada, durante sua síntese proteica, absorve mais lisina do que arginina (Kagan, 1974).

Esse pico de produção de proteínas virais durante a infecção absorvendo muito mais arginina do que lisina ocorre em vários momentos do ciclo viral, mais no pico de produção, no caso do herpes vírus simples, entre 4 e 6 h pós infeção (Kaplan et al., 1970).

No exoma humano, os códons (parte do DNA) que seguem para o RNAm, possuem tríades de bases nitrogenadas que irão informar quais aminoácidos deverão estar disponíveis para a síntese proteica. São 64 códons com os códigos (tríades) dos 20 aminoácidos que devem estar disponíveis para a síntese de proteínas. O exoma humano, curiosamente, possui seis tríades de arginina (CGU, CGC, CGA, CGG, AGA, AGG) e apenas duas de lisina (AAA e AAG) (Griffith et al., 1978).

Mesmo que no exoma humano haja mais disponibilidade de arginina, já se sabe que uma célula não infectada absorve mais lisina para produção de suas proteínas enquanto uma célula sob o comando viral absorve arginina. Em relação ao exoma do HHV-1, este contém mais arginina (8,5%) do que o exoma humano (5,4%). No proteoma viral, os valores de arginina são semelhantes ao seu exoma. Em média, os resíduos de arginina, pela análise do proteoma, é de 8,6% no capsídeo, 9,0% no tegumento, 7,1 % no envelope e 8,6% nas demais proteínas A proteína HHV-1 mais rica em arginina é a proteína do tegumento US11, que consiste em 19% de arginina (Bol e Bunnik, 2015).

Se estes estudos confirmam uma quantidade maior de arginina nas proteínas virais e uma única partícula de vírus (vírion) não pode replicar ou expressar material genético (DNA, RNA) sem a disponibilidade, principalmente, de arginina (Sanchez et al., 2016), a ausência dela pode resultar em partículas virais vazias, livres de ácidos nucleicos (Tankersley, 1964; Butorov, 2015) ou partículas desnudas, sem capsídeo, com o DNA exposto às DNases do núcleo (Becker et al., 1967).

Uma vez que a arginina é importante para a multiplicação viral, sua depleção é um ponto chave no controle viral e, como já discutido, enzimas que atuem como a arginase humana,

podem ser alvos terapêuticos interessantes (Kahán et al., 1979; Sanches, 2016; Grimes et al., 2021).

A lisina também tem uma ação depletora uma vez que nos túbulos renais pode aumentar a produção de arginase 2 degradando a arginina em ornitina e uréia (Flodin, 1997; Gaby, 2006). A consequência disso é a geração de vírus não maduros pela ausência de arginina. Baseado nesta informação e com a hipótese de que a lisina também atua de forma antagônica com a arginina pela competição de receptores celulares (Jones et al., 1967; Griffith et al., 1981; Flodin, 1997; Gaby, 2006; L-lysine, 2007; Schmidt et al., 2020), alguns estudos sugerem a suplementação de lisina e redução do aporte de arginina diante de algumas infecções virais, reforçando a ação antiviral (Griffith et al., 1978; Pedrazini et al., 2007; 2018; 2021; Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021; Melano et al., 2021).

3.5 Os aminoácidos e os vírus

Outros vírus também foram investigados com a análise de sua expressão diante da presença e supressão de arginina, tanto RNA como DNA vírus, como mostrado na Tabela 1.

Resultados positivos foram citados em vários estudos com depleção de arginina em citomegalovírus (CMV), influenza A, vaccinia, SV-40, vírus do sarampo, doença de Marrek (MDHV), hepatite C (HCV), SARS-CoV-2 (Melano et al., 2021; Grimes et al., 2021) e adenoviridae (Everitt et al.,1971; Plaat e Weber, 1979; Grimes et al., 2021).

No citomegalovírus humano, com estudos em fibroblastos embrionários humanos, a arginina se mostrou necessária para a citopatogenicidade viral e para a produção de vírions infecciosos, sendo necessária no estágio inicial de replicação. A retirada da arginina do meio 24 ou 48 horas após a infecção, resultou em um declínio na produção de vírus, indicando que a presença contínua do aminoácido é necessária para a produção constante de vírus (Garnett, 1975).

Tabela 1 - Local de atuação da arginina em alguns vírus.

Autores	Vírus	Local de ação da arginina
Becker et al., 1967	HSV-1	Proteínas do núcleo capsídeo
Loh e Oie, 1969	Reovírus	Formação do capsídeo
Everitt et al., 1971	Adenovírus 1	Encapsulamento e Replicação de DNA
Archard et al., 1971	Vaccinia	Produção de DNA
Raska et al., 1972	Adenovírus 2	Encapsulamento do DNA
Romano e Scarlata, 1973	Sarampo	Na formação de vírus completos
Kagan, 1974	HSV 1	Todas as proteínas virais
Garnett, 1975	Citomegalovírus	Produção do DNA
Tan, 1977	Simian Vírus 40	Encapsulamento do DNA
Plaat e Weber, 1979	Adenovírus 2	Formação de todas as proteínas virais
Hoffman et al., 2020	SARS-CoV-2	Sítio da Furina, S1/S2 (Clivagem da S)
Melano et al., 2021	SARS-CoV-2	Aumento da infectividade celular
Melano et al., 2021	H1N1	Aumento da infectividade celular

Fonte: Autoria própria.

O adenovírus também foi investigado e a conclusão foi de que as proteínas virais produzidas na ausência de arginina são defeituosas prejudicando a formação do capsídeo e o adequado encapsulamento de DNA viral (Raska et al., 1972). Também foi sugerido que a arginina seria importante para a própria replicação do DNA viral, além de necessária para a formação do capsídeo, desde que a privação acontecesse nas primeiras 15h pós infecção (Everitt et al., 1971). O tempo para a privação foi reforçado por outro estudo que mostrou a importância de acontecer nas primeiras 20h para que interferisse em todas as proteínas virais (Plaat e Weber, 1979). Essa afirmação vai ao encontro com a informação de como a arginina é importante para a formação de todas as proteínas virais (Kagan, 1974; Plaat e Weber, 1979; Bol e Bunnik, 2015).

O vírus influenza (RNA) possui resíduos de arginina que estão presentes dentro do domínio N-terminal NS1 viral, sendo necessária para ligações em células hospedeiras. (Schierhorn et al., 2017), o que faz com que essa região possa ser um alvo terapêutico para depleção de arginina. Essa mesma observação em relação ao terminal de ligação rico em arginina tem sido feita em relação aos SARS-CoV-2 (Hoffman et al., 2020; De Almeira *et al*, 2020, Romeu e Ollé, 2021).

O vírus vaccinia (DNA), se mostrou dependente da arginina tanto para a produção de DNA no estágio precoce da replicação, como para o encapsulamento do vírion em um estágio tardio da replicação viral (Archard e Williamson, 1971). Estudos de depleção de arginina no poliomavírus (Simian vírus 40) mostram que DNA e proteínas virais podem ser sintetizados,

mas não encapsulados em vírions maduros, semelhante aos achados em adenovírus (Tan, 1977). O morbilivírus (RNA) do sarampo, não é essencialmente dependente da arginina, mas níveis baixos de arginina reduzem a progênie viral, ou seja, vírus completos (Romano e Scarlata, 1973).

O reovírus (RNA) causador da diarreia, da família reoviridae (Rotavírus), também foi observado diante de supressão de arginina e os resultados mostraram a dependência deste aminoácido na replicação. Por microscopia eletrônica, observou-se um rompimento, uma descontinuidade no capsídeo gerando partículas defeituosas, partículas vazias sem RNA e consequentemente, sem potencial viral (Loh e Oie, 1969).

Pode-se localizar estudos com o SARS-CoV-2, em vários periódicos, sobre o balanço de aminoácidos no controle da multiplicação (Melano et al., 2021), estudos com enzimas que degradam aminoácidos com ação antiviral (Grimes et al., 2021), ou a importância da arginina para os vírus chamando a atenção para alvos terapêuticos em regiões onde o aminoácido está presente e é necessário (Hoffman et al., 2020).

O efeito da arginina e lisina bem como seus derivados éster, foram testados na infecção por SARS-CoV-2. A lisina e seu derivado éster puderam bloquear com eficiência a infecção pelo vírus, *in vitro*. Em contrapartida, o derivado de éster de arginina causou um aumento significativo. Estudos sobre o mecanismo de ação da L-lisina e seu éster revelaram que os compostos interferem no desencapsulamento do vírus e não na sua fixação e acidificação endossômica. Os resultados sugerem que o éster de lisina e a L-lisina poderiam, em tese, prevenir a infecção por SARS-CoV-2 durante a fase de entrada do vírus, enquanto que a arginina pode aumentar a infecção pelo vírus, e ao mesmo tempo, fornecem um paradigma para o desenvolvimento de antivirais de amplo espectro. Foi recomendado a inclusão de suplementação de lisina além de uma ingestão reduzida de arginina para a prevenção e tratamento de infecções por SARS-CoV-2. Neste estudo, também foi citado um estudo clínico com lisina/arginina em andamento de Kagan et al. (Melano et al., 2021).

Kagan (1974), é um dos pioneiros no estudo destes aminoácidos e embora o trabalho de seu grupo, de 2020, ainda esteja no prelo, foi citado por Melano et al. (2021) chamando a atenção com resultados clínicos preliminares promissores no controle do SARS-CoV-2. Kagan et al, acompanharam um grupo de médicos, que após observarem evidências clínicas positivas da administração de lisina em 18 pacientes com COVID-19, decidiram utilizar 2 g diários de lisina profilaticamente contra o SARS-CoV-2, juntamente com outros

profissionais de saúde da equipe. Após 3 meses de terapia, com testes semanais de RT-PCR, nenhum profissional havia se contaminado. Antes do protocolo, a média de contaminação era de dois profissionais por mês. Os resultados também foram comparados com outra unidade de saúde de mesmo porte que não fez uso do aminoácido e que relatou vários casos de contaminação da equipe no mesmo período. Vários outros casos individuais com exposição positiva confirmada, mostraram que a lisina foi excelente como profilaxia preventiva ou pós-exposição se tomada nas primeiras 24 horas. As poucas falhas relatadas com o tratamento envolviam subdosagem, falta de aderência ao protocolo terapêutico ou às restrições dietéticas essenciais (Melano et al., 2021).

No SARS-CoV-2, a proteína spike medeia a entrada do vírus nas células hospedeiras e abriga um local de clivagem S1/S2, essencial para a infecção pulmonar célula/célula, a qual é um mecanismo diferente deste vírus pandêmico. Este local, tão importante para que ocorra a infecção célula/célula, também é dependente de arginina e isso não foi verificado em outros coronavírus (De Almeira *et al*, 2020, Romeu e Ollé, 2021). Por este local de clivagem multibásico S1/S2 ser dependente de arginina e ser essencial para a infecção por SARS-CoV-2 em humanos, essa região seria um alvo potencial para intervenção terapêutica (Hoffman et al., 2020).

Uma grande revisão sobre a depleção da arginina no controle de vírus e de tumores oncogênicos foi previamente publicada. Embora a depleção de arginina já seja proposta há muito tempo, ainda não foi efetivamente aplicada à clínica médica. Como outros vírus, o SARS-CoV-2 depende obrigatoriamente de reações químicas e nutrientes do hospedeiro para a síntese de macromoléculas virais. A privação de nutrientes essenciais, uma abordagem usada no campo da oncologia para tratar tumores, pode interferir na replicação viral. Embora essa abordagem de inanição metabólica ainda não tenha sido aplicada clinicamente ao controle do vírus, estudos pré-clínicos apoiam esse conceito. A arginina é um nutriente chave que se mostra essencial *in vitro* no ciclo de vida de muitos vírus de DNA e RNA. De acordo com os resultados dos estudos analisados, a arginina pareceu ser um metabólito importante para a replicação viral bem-sucedida do SARS-CoV-2. Além disso, a arginina também é um substrato chave na resposta inflamatória do hospedeiro e a redução dos níveis séricos de arginina no plasma poderia atenuar plausivelmente a resposta inflamatória grave na infecção por SARS-CoV-2. Esse mesmo estudo discuti a depleção de arginina por meio de enzimas semelhantes a arginase concluindo que a

redução dos níveis sistêmicos de arginina seria um caminho promissor de estudos contra a COVID-19 (Grimes et al., 2021).

O efeito terapêutico de um complexo vitamínico contendo 500 mg de lisina prescrito a 53 pacientes expostos ao SARS-CoV-2 foi comparado com 60 indivíduos também expostos, mas que não fizeram uso do complexo. A diferença entre os grupos foi marcante durante as 20 semanas do estudo. Menos de 4% dos pacientes do grupo teste apresentaram sintomas semelhantes aos da gripe ou RT-PCR positivo, enquanto 20% do grupo de pacientes que não usaram apresentou sintomas semelhantes aos da gripe e 15% foram positivos para COVID-19. A abordagem antiviral foi de baixo custo e prontamente implementada, concluindo que o tratamento poderia ser complementar á outros e mais uma ferramenta útil no combate à pandemia. Foi sugerido que a inclusão da lisina auxiliou na melhora da função do sistema imunológico tanto de forma independente como auxiliando a absorção de zinco, um outro componente importante ao sistema imunológico. O mecanismo de aprimoramento imunológico pelo qual a suplementação de L-lisina reduziria as taxas de infecção seria, além do mecanismo de absorção de zinco, devido também a contagem aumentada de células T-CD4 (Margolin et al., 2021).

Os coronavírus SARS-CoV-2 pertencem à grande família Coronaviridae e várias cepas patogênicas humanas (HCoV) são conhecidas por causar principalmente doenças respiratórias. A grande maioria delas contribui para doenças do tipo resfriado, mas outras, SARS-CoV e MERS-CoV, levam a infecções graves. Essas variantes podem levar a infecções fatais com cerca de 10% e 39% de mortalidade, respectivamente. Um medicamento contendo L-lisina (L), ácido acetilsalicílico (AAS) e guanina (G) - LASAG, vendido como “Aspirina i.v. 500mg®” para tratamento de dor aguda, enxaqueca e febre, foi testado em coronavírus *in vitro.* Era sabido que o AAS já havia inibido a atividade viral do citomegalovírus e do rinovírus. Os resultados dos testes com esse composto mostraram diminuição na propagação de diferentes CoV, incluindo o MERS-CoV. O LASAG induziu títulos virais reduzidos, redução de proteína viral assim como interferiu na síntese de RNA viral, na transcrição e na replicação do vírus. Sais de ácido acetilsalicílico com aminoácidos básicos se tornam mais ativos e mais estáveis, melhorando a cinética e a dinâmica terapêutica, sendo uma abordagem com baixo potencial para levar à resistência viral oferecendo a possibilidade de aplicações antivirais de amplo espectro. Como o AAS é pouco solúvel, associar os aminoácidos básicos, lisina e glicina poderia potencializar o AAS, tornando-o mais hidrossolúvel, podendo ser inclusive injetado.

Após absorvido e metabolizado, o composto resulta em 3 compostos livres no plasma (AAS, Lisina e Glicina) (Müller et al., 2016). Esse trabalho não explorou o fato da lisina livre poder ter auxiliado ainda mais no controle da replicação viral dos coronavírus.

3.6 Protocolo com a L-lisina

A lisina é prescrita como suplemento alimentar humano normalmente na forma de cloridrato de lisina (Hayamizu et al., 2020; Matthews, 2020) administrada por via oral na forma de comprimidos ou cápsulas (Pedrazini et al., 2018; 2021).

A literatura discute as diversas doses tanto na suplementação alimentar como na profilaxia antiviral (Iwasaki et al., 2016; Schmidt et al., 2016; Mailoo e Ramps, 2017; Hayamizu et al., 2020). As doses prescritas para controle das reinfecções por HHV-1 variaram de 250 mg a 3000 mg/dia (Griffith et al., 1978; Mindell, 1986; Wright, 1994; Pedrazini et al., 2021) e em relação ao tempo de suplementação, este varia de 30 dias/ano até 3 anos (Griffith et al., 1978; 1987; McCune et al., 1984; Pedrazini et al., 2007; 2018; 2021).

A suplementação de lisina para profilaxia antiviral é segura e eficaz nas doses preconizadas (Pedrazini et al., 2007; 2018; 2021) porém, com a hipótese de antagonismo com a L-arginina (Gaby, 2006; Schmidt et al., 2020; Melano et al., 2021), um aminoácido também com funções importantes no organismo (Grimes et al., 2021, Li et al., 2021), a L-lisina deve ser suplementada por tempo limitado (Bumpstead, 2013; Mailoo e Ramps, 2017; Pedrazini e Groppo, 2021; Pedrazini e Silva, 2021; Pedrazini et al., 2021). Estudos com apenas 30 dias de suplementação de L-lisina associando uma dieta reduzida em arginina, mostraram uma redução significativa, tanto nas manifestações anuais como na gravidade das lesões (Pedrazini et al., 2007; 2018).

Uma recomendação razoável para doses suplementares é de 500-1000 mg/dia para profilaxia antiviral por tempo limitado, reservando doses mais altas de 3000 mg/dia para surtos ativos, sempre ingeridas em jejum, se possível, nos primeiros sinais do herpes simples (HHV-1/2), ou seja, nas primeiras 24 horas de manifestação, na tentativa de bloquear a evolução para a fase clínica ativa (Pedrazini et al., 2007; 2018; 2021). No caso da PR (HHV-6/7), essa dose de ataque de 3 g teria um resultado melhor se ocorresse assim que se fizesse o diagnóstico apenas com o surgimento do medalhão, mas como este pode ser confundido com lesão fúngica, o diagnóstico fica postergado. Porém, se a lisina em dose única de ataque ainda ocorrer nos primeiros 14 dias a partir do medalhão, fase em que as lesões secundárias estão surgindo

sugerindo atividade viral, ainda pode ocorrer a supressão de mais lesões secundárias e acelerar a cicatrização do medalhão e de outras lesões já existentes, o que ocorreu no caso clínico no artigo 2 (Pedrazini e Silva, 2021).

O protocolo com L-lisina para o controle da reativação dos herpes simples, desde 1998, é usado por tempo limitado (30 dias) e geralmente nos períodos onde algum gatilho de reativação poderá estar presente como exposição ao frio, ao sol, ao estresse ou quando se nota um abuso de alimentos com aminoácido arginina. Em todos esses anos de uso deste aminoácido em algumas manifestações de herpesvírus, não se teve conhecimento de nenhum efeito adverso nos pacientes tratados e muito deles foram acompanhados por no mínimo 8 anos (Pedrazini et al., 2018).

Esse protocolo para herpes simples (L-lisina em dose de ataque mais a suplementação por 30 dias, juntamente com a supressão de arginina alimentar ou suplementar) foi estipulado a partir das orientações de Mindell (1986) e de Griffith et al. (1978), mas vale lembrar que doses podem ser ajustadas a depender da idade, peso e gravidade das lesões.

O protocolo para PR, baseado nos estudos com herpes simples, também contemplou a dose de ataque única de 3g dentro dos primeiros 14 dias e doses de 500 mg/dia por 30 dias no adulto (Pedrazini e Silva, 2021). No caso da criança, as doses foram 250 mg/dia, sem dose de ataque, dose ajustada junto ao dermatologista e ao pediatra responsáveis pelo caso (Pedrazini e Groppo, 2021) e, posteriormente, confirmada na literatura.

Pesquisadores relatam que nas crianças, as doses seguras administradas para suplementação alimentar, variam bastante sendo de 53 mg/dia a 459 mg/dia em idades que variavam de 2 a 10 anos (Hayamizu et al., 2020). Porém, a dose de 250mg/dia foi a mais utilizada sendo administrada em 211 crianças de 5 a 15 anos, por 9 meses, sem que houvesse nenhuma intercorrência (Vinod e Rajagopalan, 2006). Diante das orientações médicas e com respaldo na literatura já citada, a dose de 250 mg/dia usada no paciente do artigo 1 (Pedrazini e Groppo, 2021) foi eficaz e segura melhorando o estado geral da criança ao melhorar o prurido e reduzir o ciclo total da manifestação da pitiríase rósea.

Ainda não há um consenso em relação à administração oral em jejum (Mindell, 1986; Singh et al., 2011, Pedrazini et al., 2021) ou com alimentos (Flodin, 1997; Bumpstead, 2013; Castro et al., 2019) sendo sugerido que a tomada com ou separadamente das refeições, fosse mais investigada uma vez que poderia interferir na farmacocinética podendo diferir entre esses dois modos de administração (Flodin, 1997). Todos esses fatores precisam ser estudados

para se calcular qual seria o protocolo de melhor eficácia com menor risco, porém como se quer a depleção da arginina, não seria apropriado que a suplementação de lisina com objetivo antiviral fosse realizada junto com as refeições pois como a arginina é proteinogênica (Nelson e Cox in Lehninger, 2017), ela estaria competindo com a lisina pelos mesmo carreadores, o que poderia prejudicar a absorção da lisina prejudicando o objetivo antiviral do protocolo.

Importante lembrar que tanto a L-lisina como a L-arginina são aminoácidos essenciais ao funcionamento do organismo (Bumpstead, 2013; Nelson e Cox, 2017; Hayamizu et al., 2020; Matthews, 2020, Li et al., 2021) e qualquer suplementação ou depleção devem ser sob orientação de um profissional de saúde. (Bumpstead, 2013; Schmidt et al., 2020; Bouchereau e Schiff, 2020)

A literatura lista alguns cuidados em relação ao uso deste aminoácido em altas doses ou por tempo prolongado (Bumpstead, 2013). Existe um único caso na literatura descrevendo uma síndrome de falência renal em adultos após 5 anos de uso contínuo de 3 g/dia porém a paciente também fazia uso de ibuprofeno e outras medicações pelo mesmo período e os autores sugerem a lisina como hipótese da falência baseado em estudos em ratos e estudo da lisina associada com aminoglicosídeos (Lo et al., 1996) o que pode deixar um questionamento em relação a essa hipótese.

Mais estudos devem ser realizados em relação ao uso por tempo limitado em cardiopatas que não estejam usando suplementos de cálcio (Tomblin e Lucas, 2001), em pacientes que talvez tenham alguma restrição em relação à problemas renais e hepáticos Flodin, 1997; Drug.com, 2021) ou em pacientes com HIV positivo (Butorov, 2013; 2015; 2017). A única contraindicação absoluta da suplementação com L-lisina, são os pacientes com erros inatos do metabolismo (Schimidt et al., 2020; Bouchereau e Schiff, 2020).

Existe uma necessidade enorme de modalidades terapêuticas que possam ser prontamente usadas pela população para que se tente evitar ou reduzir as manifestações dos herpesvírus. A L-lisina é uma alternativa segura, eficaz e sem custo elevado e com o controle das reativações, danos aos tecidos e órgãos serão evitados.

A propagação e a gravidade da SARS-CoV-2 também justificam mais estudos com a L-lisina para esse vírus assim como para outros vírus que venham a surgir no futuro. Da mesma forma que se preconiza uma ação antiviral nos estágios iniciais das infeções por herpesvírus, as medidas preventivas e tratamentos em estágio inicial da COVID-19 devem ser sempre consideradas por atenuarem o imediatismo da demanda por novas vacinas para novas

variantes ou por medicamentos muitas vezes de difícil acesso para muitos. Concordando com Melano et al. (2021), enquanto mais estudos não são desenvolvidos, o balanço arginina/lisina deveria ser mais observado em meio a pandemia de COVID-19.

4 CONCLUSÃO

A L-lisina tem potencial para controlar, pelo seu possível antagonismo com o aminoácido L-arginina, a gravidade dos surtos de recidivas de alguns herpesvírus como o citomegalovírus, herpes vírus simples e roseovírus. Por consequência, a terapia com o aminoácido poderia reduzir a chances da cegueira por ceratites, encefalites e Alzheimer, doenças que são potencializadas pelas recidivas dos herpesvírus.

O protocolo com L-lisina poderia ainda ser benéfico para os pacientes acometidos pela COVID-19, por inibir a arginina e consequentemente a produção de óxido nítrico, um gatilho da tempestade de citocinas. Essa hipótese deve ser objeto de estudos controlados mais aprofundados.

A L-lisina poderia ser promissora na profilaxia contra o SARS-CoV-2, pois poderia competir com a arginina na formação da proteína S do vírus durante a replicação viral.

O efeito do controle da ingestão do aminoácido arginina ou sua depleção também merece ser investigado em estudos futuros como possível benefício antiviral durante contaminações. O balanço lisina/arginina na alimentação deve ser considerado para os portadores de vírus latente como naqueles em atividade viral, pois também pode contribuir no controle de recidivas como na gravidade das infeções ativas.

Mais estudos clínicos randomizados em larga escala são necessários sobre o balanço dos aminoácidos e outros vírus de interesse.

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ANEXOS

Anexo 1 - Certificado de dispensa pelo CEP-FOP

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Piracicaba, 21 de outubro de 2021.

Ilma. **Maria Cristina Pedrazini**,
Doutoranda no PPG de Odontologia da
FOP/UNICAMP

Prezada Maria Cristina,

Após analisar a documentação apresentada ao CEP-FOP, com respeito ao projeto de pesquisa intitulado **"Efeito do aminoácido L-lisina sobre a pitiríase rósea"**, da pesquisadora **Maria Cristina Pedrazini** (Doutorando no PPG em Odontologia, Área

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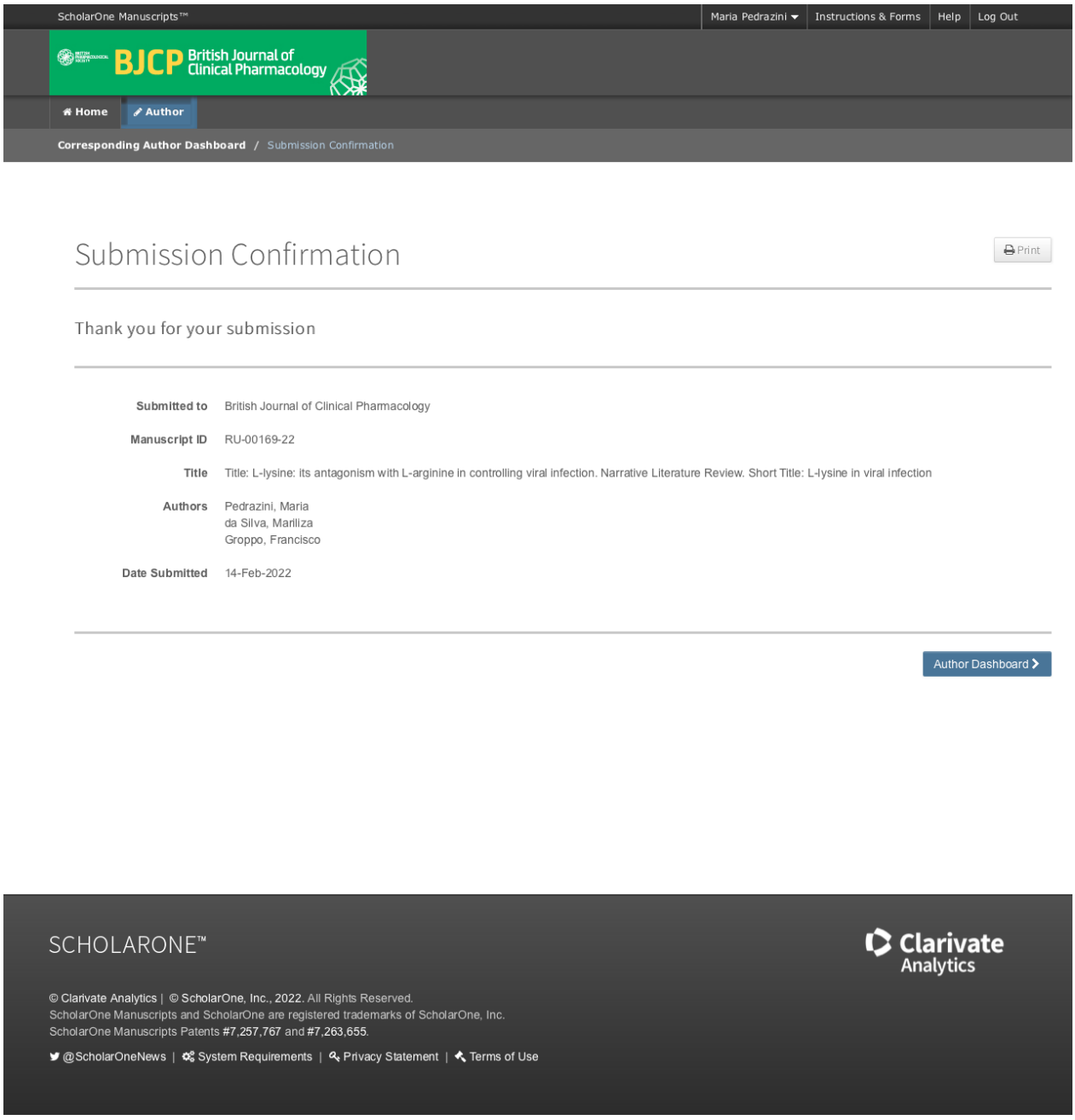
Anexo 4 – Comprovante 1 gerado na submissão do Artigo 2.3

Title: L-lysine: its antagonism with L-arginine in controlling viral infection. Narrative Literature Review.
Short Title: L-lysine in viral infection

Journal:	*British Journal of Clinical Pharmacology*
Manuscript ID	Draft
Manuscript Type:	Review Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Pedrazini, Maria; Universidade Estadual de Campinas Faculdade de Odontologia de Piracicaba, Biosciences; Faculdade de Odontologia e Centro de Pesquisas Odontologicas Sao Leopoldo Mandic, da Silva, Mariliza; São Paulo State Health Department, Department of Infectology Diagnosis Groppo, Francisco ; Universidade Estadual de Campinas Faculdade de Odontologia de Piracicaba, Biosciences
Key Words:	virology < Infectious diseases, Infectious diseases, Pharmacokinetic-Pharmacodynamic < Pharmacodynamics, Clinical Pharmacy < Clinical Pharmacology, Nutraceuticals < Nutrition
Abstract:	Knowledge about viral characteristics, mechanisms of entry into the host cell and multiplication/dissemination can help in the control and treatment of viral pathologies. Several nutritional factors linked to the host may favor viral multiplication and their control, may lead to new prophylactic alternatives and/or antiviral therapies. The objective of this review is to discuss the relationship between the amino acid L-lysine and the control of viral infections, aiming at a possible therapeutic property. This research used databases such as PubMed, Web of Science, Scielo, Medline and Google Scholar, as well as searching for articles cited by journals. Textbooks were also included in the absence of information in the cited articles. The time frame covered the period between 1964 and January 2022. The observed studies have shown that the usual antiviral therapies are not able to interfere with the viruses in their latent state, however, they can interfere with the adhesion and fusion of viral particles or the formation of proteins, which play an important role in viral epidemiology and control, particularly in the initial moment and in the reactivation. Lysine is an amino acid that can interfere in some of these phases by antagonizing another amino acid, arginine, and also by promoting the increase of arginase, increasing the catabolism of arginine, which is an essential amino acid for some viruses. Although there is evidence of the importance of these amino acids in viral control, more studies are needed, with a view to new antiviral therapies.

Anexo 5 - Comprovante 2 gerado ao final da submissão do Artigo 2.3



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Authors	Pedrazini, Maria da Silva, Mariliza Groppo, Francisco
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