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Impacto do Status de Citomegalovírus na Resposta Inflamatória ao Exercício de Alta Intensidade em Homens Fisicamente Ativos

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Dedicatória

À minha família, pelo incentivo durante minha jornada. Ao meu amor, por estar ao meu lado em todos os momentos. Aos meus orientadores, pela orientação sábia, paciência e por sempre desafiar-me a ser melhor. À Deus, por me conceder força.

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Epígrafe

As pessoas vivem apegadas àquilo que traduzem como correto e verdadeiro, assim elas definem a realidade. Mas o que significa correto e verdadeiro? Meramente conceitos vagos e subjetivos... A realidade deles pode muito bem ser uma miragem. Podemos considerar que todos simplesmente vivem em seu próprio mundo, amarrados e cegos por suas crenças, não acha? (Uchiha, Itachi)

RESUMO

As infecções do trato respiratório superior são muito comuns em atletas que realizam esforços extenuantes em alto volume e por um longo período, resultando em diminuição na qualidade do treinamento físico, consequentemente, prejudicando a performance durante a competição. Foram recrutados 22 homens saudáveis e fisicamente ativos (25,3 ± 1,4 anos) e divididos em dois grupos: CMV positivo e CMV negativo. Os participantes preencheram questionários médicos e de atividade física, realizaram avaliações antropométricas, testes de exercício cardiopulmonar e realizaram um exercício intervalado de alta intensidade (HIIT). Amostras de sangue foram coletadas antes e após o exercício, e células mononucleares de sangue periférico (PBMCs) foram isoladas para análises adicionais. As concentrações de purinas à base de adenina e os níveis de lipopolissacarídeos (LPS) foram medidos utilizando cromatografia líquida acoplada à espectrometria de massa para avaliar a sinalização purinérgica e os marcadores inflamatórios. Os resultados apresentaram interações significativas entre o tempo de exercício e o status CMV em LPS e IL-1β. O exercício aumentou significativamente os níveis de LPS em ambos os grupos (CMV+ e CMV-), mas não houve diferença entre eles. Para IL-1β, o exercício resultou em um aumento significativo apenas no grupo CMV+, com níveis pós-exercício significativamente maiores em comparação ao grupo CMV-. Não houve interação significativa para as variáveis Adenosina, ATP, AMP, ADP, PGE-2 e CK. Entretanto, o status CMV influenciou os níveis de PGE-2, sendo maiores no grupo CMV+, enquanto o exercício aumentou significativamente os níveis de CK em ambos os grupos. Esses achados sugerem que a infecção por CMV pode modular a resposta inflamatória, principalmente em IL-1β, após o exercício físico, enquanto os efeitos sobre outros parâmetros purinérgicos e inflamatórios foram mais homogêneos entre os grupos. Os resultados indicam que a infecção por CMV modula a resposta inflamatória ao exercício físico, particularmente nos níveis de IL-1β, que aumentam significativamente em indivíduos CMV+. Em contraste, outros parâmetros purinérgicos e inflamatórios apresentaram respostas mais homogêneas entre os grupos, sugerindo que o impacto do CMV é específico para certos marcadores inflamatórios.

Palavras-chave:Citomegalovírus, Atletas, Exercício de Alta Intensidade, Inflamação, Marcadores Inflamatórios, Sinalização Purinérgica

ABSTRACT

Upper respiratory tract infections are very common in athletes who engage in strenuous efforts at high volume and over long periods, resulting in decreased quality of physical training, consequently impairing performance during competition. Twenty-two healthy and physically active men (25.3 ± 1.4 years) were recruited and divided into two groups: CMV positive and CMV negative. Participants completed medical and physical activity questionnaires, underwent anthropometric assessments, cardiopulmonary exercise tests, and performed a high-intensity interval training (HIIT) session. Blood samples were collected before and after exercise, and peripheral blood mononuclear cells (PBMCs) were isolated for further analysis. Adenine-based purine concentrations and lipopolysaccharide (LPS) levels were measured using liquid chromatography-mass spectrometry to assess purinergic signaling and inflammatory markers. The results showed significant interactions between exercise time and CMV status for LPS and IL-1β. Exercise significantly increased LPS levels in both groups (CMV+ and CMV-), but there was no difference between them. For IL-1β, exercise resulted in a significant increase only in the CMV+ group, with post-exercise levels significantly higher compared to the CMV- group. No significant interaction was found for Adenosine, ATP, AMP, ADP, PGE-2, and CK. However, CMV status influenced PGE-2 levels, which were higher in the CMV+ group, while exercise significantly increased CK levels in both groups. These findings suggest that CMV infection may modulate the inflammatory response, particularly in IL-1β, after physical exercise, while the effects on other purinergic and inflammatory parameters were more homogeneous across groups. The results indicate that CMV infection modulates the inflammatory response to physical exercise, particularly in IL-1β levels, which increase significantly in CMV+ individuals. In contrast, other purinergic and inflammatory parameters showed more homogeneous responses between groups, suggesting that the impact of CMV is specific to certain inflammatory markers.

Key words: Cytomegalovirus (CMV), Athletes, High-Intensity Exercise, Inflammation, Inflammatory Markers, Purinergic Signaling.

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LISTA DE ABREVIATURAS E SIGLAS

ADP - Adenosina difosfato
AMP - Adenosina monofosfato
ATP - Adenosina trifosfato
CK - Creatina quinase
CMV - Citomegalovírus
CPX - Teste de exercício cardiopulmonar
EBV - Epstein Barr
HIIT - Treinamento intervalado de luta intensidade
HLA - Human like receptor
HIV - Vírus da Imunodeficiência humana
HRMAX - Frequência cardíaca máxima
IL-1B - Interleucina - 1 beta
IL-6 - Interleucina-6
ITRS - Infecção trato respiratório superior
KIRS - Immunoglobulin-like receptor
LPS - Lipopolissacarídeo
MHC - Complexo histocompatibilidade
NK - Natural Killers
PBMCS - Células mononucleares do sangue periférico
RPE - Escala de percepção de esforço
VO2MAX - Consumo máximo de oxigênio

SUMÁRIO

1. INTRODUÇÃO

A depleção do sistema imunológico em atletas é uma preocupação comum devido à natureza intensa e exigente do treinamento e competição de alto nível. O conceito de curva em J é utilizado no contexto do treinamento físico e descreve a relação entre a carga de treinamento e a resposta/adaptação do organismo (Nieman, 1994). Essa teoria sugere que a atividade física extenuante pode desencadear uma resposta imune alterada, potencialmente levando a uma janela temporária de maior suscetibilidade a infecções (Nieman, 1994; Peters et al., 1993).

Inicialmente, quando o treinamento é aplicado, ocorre uma fase de adaptação positiva, em que o organismo responde de maneira favorável ao estímulo do treinamento (Nieman, 1994; Peters et al., 1993). Nessa fase, há melhorias no desempenho, na capacidade física, no aumento da força, resistência, entre outros aspectos relacionados ao objetivo do treinamento. No entanto, à medida que a carga de treinamento continua a aumentar de forma excessiva ou sem adequada recuperação, pode ocorrer uma fase de sobrecarga negativa (Nieman, 1994; Peters et al., 1993). Nessa fase, o organismo não consegue se recuperar adequadamente dos estímulos do treinamento, levando a uma redução no desempenho, fadiga persistente, maior risco de lesões e uma maior susceptibilidade a infecções respiratórias (Nieman, 1994; Peters et al., 1993; Nieman, 1997).

Durante exercícios extenuantes e prolongados, ocorre uma imunodepressão induzida pelo exercício com origem multifatorial (Malm, 2006). Essa supressão temporária do sistema imunológico é conhecida como “Janela aberta”. Autores já relataram na literatura que essa exposição eleva o número de neutrófilos circulantes e diminui os linfócitos sanguíneos, levando a um comprometimento da fagocitose, diminuindo a eficiência do sistema oxidativo e a atividade citolítica de células Natural Killers (Pedersen & Ullum, 1994). Isso pode levar a um aumento do risco de infecções do trato respiratório superior por patógenos oportunistas (Nieman et al., 2012).

O citomegalovírus (CMV) é um vírus da família Herpesviridae que afeta uma grande parte da população mundial. Trata-se de um vírus comum e oportunista, que pode permanecer latente no organismo após a infecção inicial

e ser reativado em momentos de supressão imunológica (Virgin, Wherry & Ahmed, 2009). Comparado com outros herpesvírus, o CMV tem um genoma muito grande e divergente, o que lhe permite escapar à detecção imunológica e parece persistir em monócitos e células progenitoras mieloides CD34+ (Virgin, Wherry & Ahmed, 2009).

A detecção precoce e o diagnóstico preciso da infecção por CMV são essenciais para um manejo adequado e para a implementação de medidas preventivas (McDonald, 1997). Os métodos comuns de diagnóstico incluem a detecção de anticorpos específicos (IgM e IgG) e a análise do DNA viral em amostras de sangue ou urina, mas estes métodos têm limitações em termos de sensibilidade e especificidade (McDonald, 1997).

No ambiente esportivo, onde os atletas estão sujeitos a um intenso treinamento físico e contato próximo com outros competidores, a infecção por CMV pode representar um desafio adicional (Fricker et al., 2000). A transmissão do CMV ocorre principalmente por meio do contato com fluidos corporais infectados, como saliva, urina, sangue e secreções genitais. Assim, o risco de infecção aumenta devido ao compartilhamento de equipamentos esportivos, contato físico direto e exposição a ambientes fechados.

A infecção por CMV em atletas pode ter implicações significativas para sua saúde e desempenho esportivo (Fricker et al., 2000; Chang & Barry, 2010). Estudos têm demonstrado que a infecção aguda pelo CMV pode resultar em sintomas semelhantes aos da mononucleose infecciosa, incluindo fadiga, febre, mal-estar e comprometimento do desempenho físico (Fricker et al., 2000; Chang & Barry, 2010). Esses efeitos podem resultar em um tempo de recuperação mais prolongado e comprometer o rendimento esportivo (Fricker et al., 2000; Chang & Barry, 2010).

Portanto, compreender a prevalência, os sintomas e as consequências da infecção por CMV em atletas é de suma importância para implementar medidas preventivas e estratégias de manejo adequadas. O presente estudo tem como objetivo analisar a prevalência da infecção por CMV em atletas e investigar seus efeitos sobre a saúde e o desempenho esportivo, fornecendo informações relevantes para a promoção da saúde e bem-estar dos atletas.

1.1. Infecções Latentes

Infecção viral latente é um estado em que um vírus infecta uma célula ou um organismo, mas não se replica ativamente ou causa sintomas imediatos. Em vez disso, o vírus entra em um estado de "latência" ou "dormência" dentro das células hospedeiras, onde permanece inativo e oculto do sistema imunológico e das medidas tradicionais de detecção (Cohen, 2020).

Durante a fase latente, o material genético do vírus (geralmente DNA) é incorporado ao genoma da célula hospedeira ou permanece como um episoma, sem produzir novas partículas virais ou causar doença aparente (Hara et al., 2002). Essa infecção pode durar longos períodos, até mesmo a vida inteira do hospedeiro (Rostgaard et al., 2019). Fatores como estresse ou supressão do sistema imunológico podem reativar o vírus, levando à síntese de novas partículas virais e a manifestações recorrentes ou crônicas.

Vírus como herpes simplex (HSV), varicela-zoster, Epstein-Barr (EBV) e citomegalovírus (CMV) estabelecem relações de longo prazo com os hospedeiros até que a reativação ocorra (Frank et al., 2022). Esses vírus apresentam complexidades notáveis em suas estruturas, organização genômica e estratégias de infecção, incluindo genomas quiméricos (Goodrum, 2021).

É importante sublinhar que, mesmo durante o período latente, esses vírus têm o potencial de serem transmitidos a terceiros, mesmo quando o hospedeiro aparenta estar saudável e assintomático (Khan et al., 2020; Goodrum, 2021). A exploração da infecção viral latente assume uma importância crucial para a compreensão da persistência desses vírus no organismo e para o desenvolvimento de estratégias visando prevenir a reativação e a disseminação (Khan et al., 2020; Goodrum, 2021).

1.2. Citomegalovírus e sistema imunológico

O CMV é um vírus β-herpes amplamente disseminado, cuja prevalência de infecção varia de acordo com a idade, etnia e localização geográfica (Khan et al., 2020). Nos Estados Unidos, ele infecta uma grande porcentagem da

população adulta (40-70%), enquanto a taxa global pode variar de 45% a 100% (Khan et al., 2020).

A infecção pelo CMV, em geral, transcorre de maneira assintomática ou apresenta sintomas leves em indivíduos saudáveis (Sissons e Wills, 2015). Comparado com outros herpesvírus, o CMV possui um genoma muito grande e divergente, o que permite escapar à detecção imunológica e parece persistir em monócitos e células CD34+ (Wang et al., 2009; Sang et al., 2021). Entretanto, em populações com imunossupressão, como transplantados, portadores do HIV ou aqueles acometidos por patologias que comprometem a resposta imunológica, o CMV surge como uma das principais causas de morbidade e mortalidade nessa população específica (Sang et al., 2021). Além disso, o vírus possui uma reativação periódica, causando uma reativação de células TCD8+ e células natural killers (NK) (Weinberger et al., 2007).

Independentemente da idade, as pessoas com infecção latente de CMV apresentam números e proporções aumentados de células TCD8+ com um fenótipo altamente diferenciado que pode durar por diversos meses (Van Leeuwen et al., 2002). As células TCD8+ e TCD4+ desempenham um papel central na resolução de infecções e na manutenção da memória imunológica de longo prazo durante a persistência viral (Almanzar et al., 2005; Sylwester et al., 2005). A citotoxicidade do CMV é predominante em células TCD8+, embora as TCD4+ também tenham a capacidade de lisar células alvo infectadas (Appay et al., 2002). Estudos publicados recentemente demonstraram que a infecção latente por CMV aumenta a proporção de células NK que expressam o receptor de ativação NKG2C (Lopez-Vergès et al., 2011). As células NK expressam uma gama de receptores inibitórios e excitatórios em sua superfície celular que regulam a sua atividade citotóxica (Gumá et al., 2004). Dentre eles estão os Immunoglobulin-like receptors (KIRS), que são capazes de fornecer sinais inibitórios e/ou de ativação às células NK através do HLA (human leukocyte antigens) expressos em células hospedeiras saudáveis e transformadas em células alvo (Cosman et al., 2001). As células NK desempenham um papel crucial no combate ao CMV e outras infecções virais em imunocomprometidos através da expressão de uma série de receptores de ativação (NKG2C, DNAM-1 e NKp46), que estão aumentados em doadores de sangue CMV+, sugerindo

que estes ativadores estão envolvidos na resposta contra o CMV (Magri et al., 2011; Junger, 2011).

1.3.Sistema imune do atleta

O sistema imunológico de um atleta desempenha uma função vital na preservação da saúde geral e na otimização do desempenho esportivo (Gleeson, 2007). Entretanto, a prática de exercícios intensos e prolongados pode induzir efeitos tanto benéficos quanto prejudiciais no sistema imunológico, uma vez que a complexa interação entre células específicas, citocinas e vias metabólicas é suscetível a modulações sutis (Gleeson, 2007).

É amplamente reconhecido que o exercício regular de intensidade moderada confere benefícios ao organismo, promovendo uma resposta imune equilibrada. Porém, períodos prolongados de treinamento intensivo podem gerar uma depressão no sistema imunológico, destacando a necessidade de uma análise detalhada das respostas imunes associadas a diferentes modalidades de exercício (Gleeson, 2007).

As respostas imunes desencadeadas pelo exercício são altamente organizadas, com células imunes específicas sendo redistribuídas para desempenhar funções definidas, mediadas por complexas interações entre citocinas (Jones & Davison, 2018).

Os estudos que investigam os efeitos do exercício no sistema imunológico abrangem tanto os efeitos crônicos do treinamento físico quanto às respostas agudas ao exercício, aprofundando a compreensão das intrincadas interações celulares e moleculares (Gleeson, 2007; Jones & Davison, 2018). Tanto o exercício agudo quanto o crônico demonstraram ter um impacto significativo na redistribuição, atividade, tráfego e função dos leucócitos, células-chave no sistema imunológico (Jones & Davison, 2018).

Foi documentado que a intensidade, duração e volume do exercício influenciam de maneira substancial a redistribuição das células imunes na circulação durante o exercício, sinalizando a complexidade das vias metabólicas envolvidas nesse processo (Jones & Davison, 2018).

1.4. Infecções do trato respiratório superior em atletas

Para os atletas, as infecções do trato respiratório superior (ITRS) exercem impactos de magnitude considerável no desempenho atlético e na rotina de treinamento (Nieman et al., 1990). A incidência de ITRS em atletas de alto rendimento pode aumentar durante períodos de treinamento intenso, em associação a aumento de volume de treino e competições (Nieman et al., 1990). Dados coletados durante competições internacionais revelam que 7% (2-16%) dos atletas de elite apresentam episódio de doença respiratória, sendo a principal apresentação clínica e a de diagnóstico mais comum (Alonso et al., 2010; Engebretsen et al., 2013; Mountjoy et al., 2010). A suscetibilidade exacerbada desses indivíduos a tais infecções é multifacetada, associada a fatores como uma exposição intensificada, particularmente para aqueles que se exercitam em ambientes fechados ou em grupo, conferindo maior propensão à exposição a germes e vírus veiculados por gotículas respiratórias (Peters et al., 1993).

O treinamento físico vigoroso e prolongado, por sua vez, pode temporariamente comprometer a eficácia do sistema imunológico, ampliando a vulnerabilidade dos atletas a infecções, devido à supressão imune, resultando na reativação temporária do vírus, provavelmente devido a um declínio induzido pelo exercício nas células TCD8+ (Walsh et al., 2011; Reid et al., 2004; Gleeson et al., 2002). É descrito na literatura que o exercício intenso diminui a expressão de receptores toll-like e aumenta a produção de cortisol, epinefrina e IL-6, fazendo com que haja uma diminuição da resposta mediada por células Th1. Também, há alteração na função de células NK, linfócitos T e B, produção de IgA salivar, MHC II e outros biomarcadores imunológicos por diversas horas do dia (Shaw et al., 2017). Além disso, atletas que frequentemente se deslocam para competições estão suscetíveis a diferentes vírus em locais diversos, amplificando o risco de infecções (Peters et al., 1993; Valtonen et al., 2021).

Os sintomas comuns associados à ITRS incluem coriza, espirros, dor de garganta, congestão nasal, tosse leve e febre baixa. Embora geralmente essas infecções sejam leves e autolimitadas, para os atletas, os sintomas podem impactar o desempenho e levar a pausas nas atividades esportivas (Valtonen et al., 2021).

Para prevenir a ITRS, os atletas devem adotar rigorosas medidas de higiene, como lavar as mãos regularmente, evitar tocar o rosto e minimizar o contato com pessoas doentes. Além disso, manter um estilo de vida saudável, com uma dieta equilibrada, sono adequado e gerenciamento do estresse, é fundamental para fortalecer o sistema imunológico (Pawelec et al., 2009; Turner et al., 2013).

Caso um atleta desenvolva uma ITRS, é importante buscar orientação médica para garantir um tratamento adequado e monitorar a condição. Em algumas situações, pode ser necessário repouso e redução temporária das atividades esportivas para permitir uma recuperação completa e evitar complicações (Pawelec et al., 2009).

1.5. Sistema purinérgico e exercício físico:

O sistema purinérgico é um conjunto de vias de sinalização celular que utiliza nucleotídeos de purina, como trifosfato de adenosina (ATP), difosfato de adenosina (ADP) e monofosfato de adenosina (AMP) (Idzko et al., 2014). A liberação de ATP intracelular em resposta a condições hipóxicas ou inflamadas por células intactas, ativadas ou moribundas é o primeiro passo da sinalização purinérgica (Di Virgilio et al., 2015), que regula diversas respostas imunológicas essenciais, começando com a quimiotaxia de neutrófilos e macrófagos, passando pela eliminação intracelular de patógenos e a ativação da NADPH-oxidase, até a maturação e liberação de IL-1β. Além disso, ela governa a proliferação de linfócitos T induzida por antígenos e a diferenciação das células T helper em Th1 e Th2 (Di Virgilio et al., 2015). O ATP extracelular desencadeia múltiplas funções efetoras imunológicas para inibir infecções e é principalmente um metabólito pró-inflamatório (Di Virgilio et al., 2017), que pode atuar tanto no nível parácrino quanto no autócrino, ativando dois tipos de receptores P2 (North, 2002).

Os receptores purinérgicos são receptores de superfície celular onipresentes que são ativados por adenosina di-(ADP) e tri-(ATP) fosfatos extracelulares (receptores P2) ou adenosina (receptores P1) (Cannon et al., 2010). Os receptores purinérgicos P2 são divididos em famílias ionotrópicas P2X e metabotrópicas P2Y. Os receptores P2X são canais iônicos controlados por

ATP, enquanto os receptores P2Y são receptores acoplados à proteína G que são ativados por nucleotídeos de adenina e uridina ou açúcares de nucleotídeos (Fischer et al., 2007; North, 2002). Além disso, os receptores P2Y regulam a concentração de Ca^{2+} através da ativação de fosfolipase C, que gera inositol trifosfato (IP3). O IP3 promove a liberação de Ca^{2+} a partir dos estoques intracelulares do retículo endoplasmático.

Estudos demonstraram que os receptores purinérgicos desempenham um papel crucial na regulação dos níveis de cálcio celular, observando-se um aumento significativo nos níveis de cálcio após infecção por citomegalovírus humano (Gumá et al., 2004). Relatos anteriores indicam que certos membros da família dos receptores purinérgicos apresentam níveis elevados de expressão em células infectadas por CMV. No entanto, o papel molecular desses receptores durante a infecção permanece insuficientemente esclarecido (Idzko et al., 2014; Di Virgilio & Vuerich, 2015).

Diversos estudos recentes indicam que um mecanismo purinérgico altamente regulado desempenha um papel crucial nas funções efetoras das células imunes e, consequentemente, no resultado da interação entre hospedeiro e microrganismo (Di Virgilio et al., 2017; Di Virgilio & Vuerich, 2015). No entanto, a importância desse mecanismo na patogênese de doenças infecciosas e as possíveis estratégias terapêuticas ainda necessitam de investigação adicional. Neste trabalho, focamos na regulação das funções efetoras das células imunes mediadas pela sinalização purinérgica em indivíduos com alta capacidade cardiorrespiratória infectados ou não por citomegalovírus.

2. OBJETIVOS

Este estudo tem como objetivo investigar as diferenças na sinalização purinérgica e nos marcadores inflamatórios em indivíduos fisicamente ativos, estratificados com base no status de infecção por citomegalovírus, ao serem submetidos a um protocolo de exercício agudo.

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ARTIGO 1

Modulation of the Inflammatory Response by Cytomegalovirus in High-Intensity Exercise: A Study of Physically Active Men

(Formatado conforme normas do periódico Medicine and science in sports and exercise – *Qualis Q1, Fator de Impacto 4,1*)

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Running title: Inflammatory Responses to Exercise in latent CMV+ Athletes

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Abstract:

This study recruited 22 healthy, physically active men (25.3 ± 1.4 years, Vo2Max 48.25±6.18), divided by CMV serostatus: CMV-positive and CMV-negative groups. Participants completed medical and physical activity questionnaires, underwent anthropometric and cardiopulmonary exercise assessments, and performed a high-intensity interval exercise (HIIE) session. The trial occurred in the morning, at least 7 days after preliminary measurements. Participants performed a 5-minute warm-up at 40% of their HRmax, followed by ten bouts of 60 seconds at 85-90% HRmax, alternating with 75 seconds of recovery at 50% HRmax. Ratings of perceived exertion (RPE) were recorded using the Borg scale, and heart rate (HR) was monitored via telemetry. Blood samples were collected pre- and post-exercise, and peripheral blood mononuclear cells (PBMCs) were isolated. Results showed significant interactions between exercise time and CMV status for LPS and IL-1β. Exercise increased LPS levels in both groups, with no difference between CMV + and CMV- groups. However, IL-1β increased significantly only in the CMV+ group. No significant interactions were found for Adenosine, ATP, AMP, ADP, PGE-2, and CK, though CMV status influenced PGE-2 levels, which were higher in the CMV+ group. Exercise significantly increased CK in both groups. These findings suggest that CMV modulates the inflammatory response to exercise by increasing IL-1β in CMV+ individuals.

Key words: Athletes, Cytomegalovirus, High-Intensity Exercise, Inflammation, Inflammatory Markers, Purinergic Signaling.

Introduction:

Cytomegalovirus (CMV) is a virus from the Herpesviridae family that affects the human immune system and can establish latent infection in the host. During periods of immunosuppression, CMV can reactivate, altering the immune response and impacting health and physical performance (1). This infection alters the phenotype of immune cells, particularly T lymphocytes and Natural Killer (NK) cells, leading to premature immune aging and increased susceptibility to other infections. Moreover, CMV seropositivity is associated with a reduction in naive CD4+ T cells and an increase in effector memory T cells (2).

Due to the intensity of their training regimens, high-performance athletes exhibit increased susceptibility to infections as a consequence of immune system overload. In the initial phases of training, the body undergoes a positive adaptation characterized by improvements in performance, strength, and endurance (3, 4). However, when training volume escalates excessively without sufficient recovery periods, harmful overload ensues, resulting in decreased performance, persistent fatigue, and an elevated risk of injuries and respiratory infections (3, 4, 5).

This overload adversely affects the immune system, leading to an increase in neutrophil count and a reduction in circulating lymphocytes, which impairs phagocytosis, the oxidative system, and natural killer (NK) cell activity (6, 7). Consequently, this heightens the susceptibility to respiratory infections caused by opportunistic pathogens (8). The interaction between cytomegalovirus (CMV), T cells, and NK cells suggests that CMV may modulate the immune response to both acute and chronic exercise, highlighting the critical role of infection history in athletic performance (9).

The purinergic signaling system, which involves nucleotides such as ATP, ADP, and AMP, is integral to regulating immune responses (10, 11). ATP release from activated or damaged cells, triggered by hypoxia or inflammation, initiates this signaling cascade, which governs key immune processes, including neutrophil and macrophage chemotaxis, pathogen clearance, activation of NADPH oxidase, and the maturation and release of IL-1β (12, 13).

Studies have shown that purinergic receptors regulate intracellular calcium levels, with a significant increase observed following CMV infection (14). Moreover, CMV infection impacts purine metabolism, particularly during acute infection. Infected cells release ATP and adenosine as damage-associated molecular patterns (DAMPs), thereby activating immune responses and contributing to inflammation (15, 16). In this context,

purine metabolites can exacerbate inflammatory conditions, playing a role in regulating body temperature and modulating cytokine release (17, 18).

Recent research indicates that the regulated purinergic mechanism is essential for immune functions and the host's and microorganisms' interaction (2, 11). However, further studies are required to fully understand its role in the pathogenesis of infectious diseases and explore potential therapeutic strategies.

Cytomegalovirus (CMV) infection has the potential to modulate the anti-inflammatory effects of exercise, though findings remain inconsistent. Exercise is generally associated with promoting anti-inflammatory responses, enhancing immune function, and reducing pro-inflammatory markers such as IL-6 and TNF-α (19, 20). However, immune responses may be altered in individuals with latent CMV infection. For example, while exercise typically elevates leukocyte counts and cytokine levels, CMV-positive individuals may not exhibit significantly different immune responses compared to CMV-negative individuals (21). Furthermore, CMV infection can induce T-cell exhaustion, potentially diminishing the immunological benefits of exercise (9). Thus, while exercise exerts anti-inflammatory effects, CMV infection may modulate these outcomes, particularly regarding T-cell functionality and cytokine regulation.

While exercise is known for its anti-inflammatory potential, CMV infection may interfere with this process, and studies have yielded inconsistent results. Generally, physical exercise tends to promote anti-inflammatory responses, enhancing immune function and reducing pro-inflammatory markers such as IL-6 and TNF-α (19, 20). However, in individuals with latent CMV infection, immune responses may differ. Although exercise increases leukocyte counts and cytokine levels, the immune response in CMV-positive individuals does not appear to differ significantly from that of CMV-negative individuals (21). Furthermore, CMV infection can induce T-cell exhaustion, which may diminish the immunological benefits associated with exercise (9). Therefore, while exercise exerts anti-inflammatory effects, CMV may modulate this impact, particularly concerning T-cell dynamics and cytokine activity.

Methodos

Twenty-two healthy men with high physical fitness levels were divided into two groups: CMV+ (age: 23.7±2.37; VO2max: 48±5.96) and CMV- (age: 24.0±3.66; VO2max: 48.50±6.47) (Table 1) were recruited from Porto Alegre, Brazil. The criteria for being classified as physically active included completing at least 3 hours of endurance training per week for a minimum of 3 years.

Before the experimental trials, all participants completed a medical health questionnaire, the International Physical Activity Questionnaire (IPAQ; link), and the Physical Activity Readiness Questionnaire (PAR-Q). The study was approved by the UFCSPA Research Ethics Committee (protocol 1.973.432). All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki 2013 guidelines.

Participants were nonsmokers, maintained a normocaloric diet, and did not take any medications or supplements that were known to affect metabolic or immune systems. Exclusion criteria included excessive alcohol intake (> ten drinks/week), autoimmune, cardiac, endocrine, or metabolic diseases, and acute or chronic infections that could impact study outcomes. All participants refrained from exercise within 48 hours of each laboratory visit and were instructed to avoid alcohol and caffeine beverages 12 hours before the lab visits.

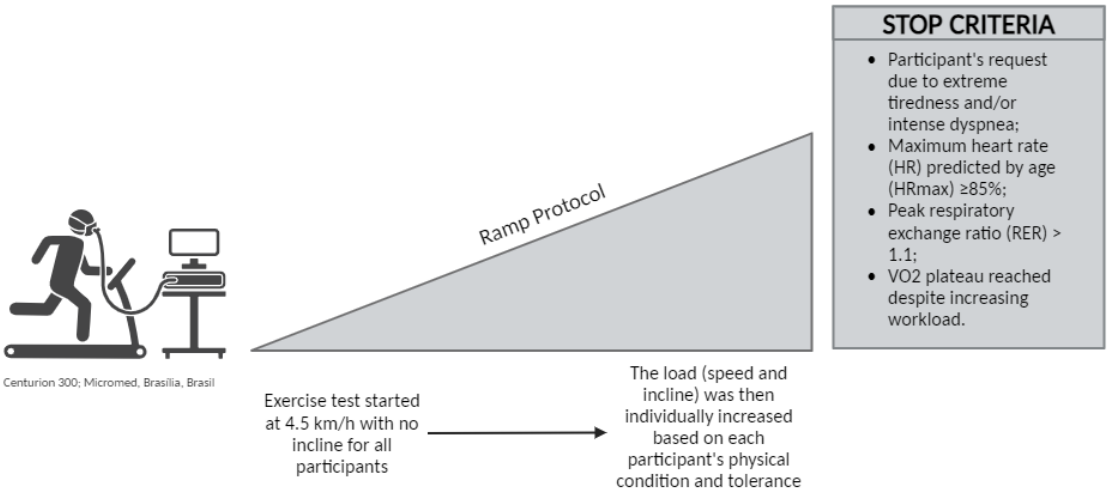
The participants came to the laboratory on three separate days, with a minimum interval of 7 days between visits, always after an overnight fast of 8 to 12 hours. They were instructed to maintain the same eating routine for the 24 hours before the test, avoid strenuous exercise 48 hours beforehand, and abstain from alcohol and caffeine consumption for the last 12 hours. During the first visit, participants completed a medical questionnaire and the International Physical Activity Questionnaire (IPAQ) and were screened to ensure they met the study's inclusion and exclusion criteria. Eligible participants returned for a second visit to undergo body composition evaluation and incremental cardiopulmonary exercise testing (CPX) (table 1). All experimental trials were conducted between 08:00 and 10:00 am, with room temperature and humidity controlled at 18-24°C and 50-70%, respectively.

A qualified professional conducted all anthropometric evaluations. Each test was performed three times, and the average value was used for analysis. Body mass (kg) and height (m) were measured using a semi-analytical scale (Welmy, Santa Barbara D'Oeste,

Brazil) with a capacity of 200 kg and a stadiometer with an accuracy of 0.1 kg and 0.005 cm, respectively. Waist circumference (WC, cm) was measured using an inelastic measuring tape (Table 1).

Using a ramp protocol, the CPX was performed on an electric treadmill (Centurion 300; Micromed, Brasilia, Brazil). The exercise test started at 4.5 km/h with no incline for all participants. The load (speed and incline) was then individually increased based on each participant's physical condition and tolerance. The test aimed to achieve VO2peak within 8 to 12 minutes, followed by 1 minute of active recovery (same speed and incline as the initial test) and 5 minutes of passive recovery. The speed and incline of the treadmill were gradually increased until the participant reached their maximum limit. The test was terminated under the following conditions: (a) participant's request due to extreme tiredness and/or intense dyspnea; (b) maximum heart rate (HR) predicted by age (HRmax) ≥85%; (c) peak respiratory exchange ratio (RER) > 1.1; (d) VO2 plateau reached despite increasing workload (Figure 1).

Figure 1: Schematic representation of the cardiopulmonary exercise testing (CPX) protocol.

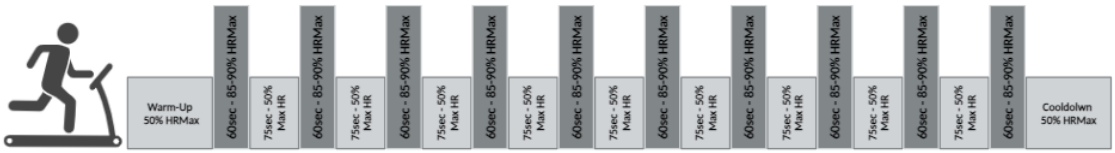


Ventilatory and metabolic parameters were collected using Metalyzer 3B (Cortex, Leipzig, Germany) and analyzed using the mean data from eight respiratory cycles. The CPX system was calibrated before each test for both airflow and O2 and CO2 analyzers. The VO2 peak was determined by averaging the last 30 seconds of the test.

The exercise trial was conducted in the morning, at least 7 days after the preliminary measurements. Participants performed a 5-minute warm-up at a workload

eliciting 40% of their maximum heart rate (HRmax). The high-intensity interval exercise (HIIE) consisted of 10 bouts of 60 seconds at 85-90% of their heart rate (MaxHR), alternating with 75 seconds of recovery at 50% MaxHR on a motorized treadmill. Ratings of perceived exertion (RPE) were monitored using the Borg scale, and heart rate (HR) was monitored by telemetry (Polar, Kempele, Finland) after each interval bout during HIIE (Figure 2).

Figure 2: Overview of the high-intensity interval exercise (HIIE) protocol.



Analysis of Adenine-based Purine Concentrations and Lipopolysaccharide (LPS) Levels by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

For the analysis, 150 µL of acetonitrile was added to 50 µL of plasma samples, followed by vigorous shaking for 60 seconds. The samples were then centrifuged at 9000g for 6 minutes. The resulting supernatant was collected, and a 25 µL aliquot was directly injected into the LC-MS/MS system. The analytical setup comprised a Nexera UFLC system connected to an LCMS-8040 triple quadrupole mass spectrometer (Shimadzu). The electrospray ionization-MS/MS parameters were configured to operate in positive and negative ion modes, with a polarity switch time of 25 ms. Specific conditions included a capillary voltage of 4500 V for positive mode and 3000 V for negative mode, a desolvation line temperature of 200°C, a heating block temperature of 500°C, a drying gas flow rate of 18 L/min, and a nebulizing gas flow rate of 2 L/min.

Analyses were conducted using multiple reaction monitoring (MRM) with the following fragmentation patterns: m/z 268.0 → m/z 136.0 for adenosine ([M + H]+), m/z 346.0 → m/z 210.1 for AMP ([M − H]−), m/z 426.0 → m/z 327.4 for ADP ([M − H]−), and m/z 506.0 → m/z 207.5 for ATP ([M − H]−). Chromatographic separation was achieved using a Shim-pack GISS column (2.1 × 100 mm, 1.9 µm particle size;

Shimadzu) with a flow rate of 0.3 mL/min. The gradient mobile phase system consisted of water (Solvent A) and acetonitrile (Solvent B), both containing 0.2% acetic acid and 0.1% tributylamine. The gradient program was as follows: 0–4.5 min: 10–90% B; 4.5–5.5 min: 90% B; 5.5–5.6 min: 90–10% B; 5.6–10 min: 10% B. The column oven was maintained at 30°C. Data acquisition and processing were performed using LabSolutions software (Shimadzu).

Additionally, the concentration of lipopolysaccharides (LPS) was determined by quantifying 3-hydroxytetradecanoic acid, following the method described by Teixeira et al. (2021).

Cytokine levels

The plasma concentrations of interleukin-1β (eBioscience, ThermoFisher) were quantified by enzyme-linked immunosorbent assay (ELISA) in a microplate reader (EzReader). The detection limits of each cytokine is 0.3 pg/ml;

Statistical analysis

To assess the existence of significant differences in the mean values of various physiological parameters (Adenosine, ATP, AMP, ADP, LPS, PGE-2, CK, and IL-1β) across different time points of exercise exposure (pre and post) and CMV group (positive and negative), a two-way repeated measures ANOVA was conducted, considering a mixed model. The assumptions of residual normality and homogeneity of variances were verified using the Shapiro-Wilk and Levene's tests, respectively. Multiple comparisons were performed using the paired t-test for repeated measures over time. Outliers were removed using the boxplot method. A significance level of $\alpha = 0.05$ was applied for all analyses. Statistical analyses were conducted using the R software (22).

Results

The table 1 presents characteristics of the study participants, the variables measured, including height (cm), age (years), body mass (kg), % fat (%), BMI (kg/m²), max HR (bpm), and VO2 max (mL/kg/min).

Table 1: Characteristics of the study participants

Variable	CMV +	CMV -
Height (cm)	1.77±0.050	1.77±0.052
Age (years)	23.7±2.37	24.0±3.66
Body mass (kg)	86.30±14.90	79.6±11
% Fat	8.8±1.13	10.4±2.49
BMI (Kg/m²)	27.4±3.85	25.4±2.61
HR Max (bpm)	186±12.60	190±17.00
Vo2 Max (mL/kg/min)	48±5.96	48.50±6.47

A two-way ANOVA was conducted to evaluate whether there is an interaction between the patient's exposure to physical exercise (pre and post) and their CMV status (positive or negative) on the mean values of the physiological parameters Adenosine, ATP, AMP, ADP, LPS, PGE-2, CK, and IL-1β.

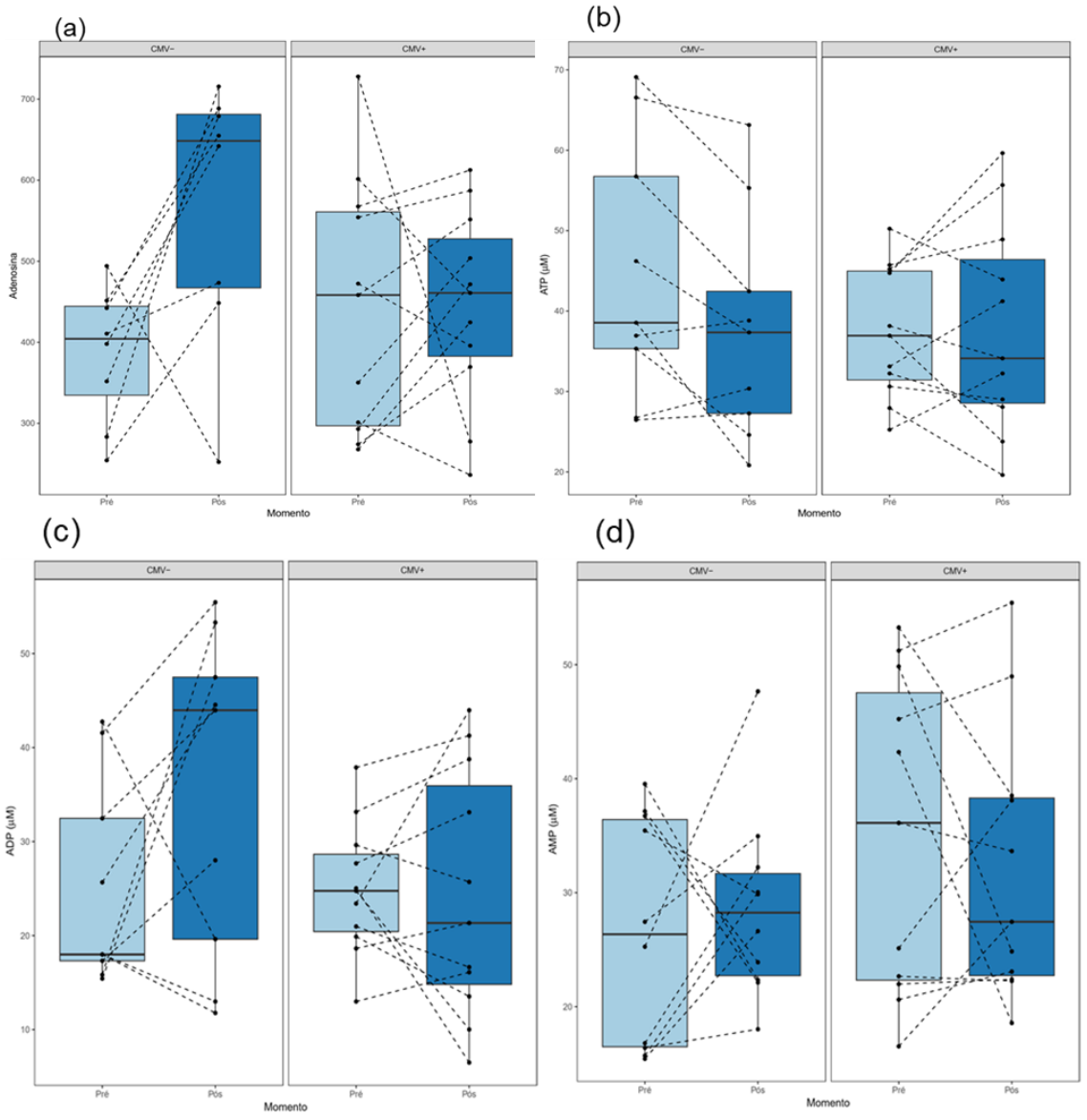
Adenosine, ATP, ADP, and AMP

The analysis revealed no significant interaction between CMV status and exercise exposure time on mean adenosine levels (Figure 3A). Furthermore, there were no significant differences in mean adenosine levels between the CMV-positive and CMV-negative groups, nor between pre- and post-exercise exposure times. Additionally, a significant decrease in the percentage change of adenosine was observed in the CMV+ group compared to the CMV- group ($p = 0.02$) (Figure 8A).

The analysis of ATP, AMP, and ADP levels (Figures 3B, 3C, and 3D) showed no significant interactions between CMV status and physical exercise. Additionally, no main effects of physical exercise or CMV group were observed for ATP. Similarly, there were no significant differences in mean AMP and ADP levels between the CMV-positive and

CMV-negative groups, nor between pre- and post-exercise exposure times. ATP levels showed a more significant reduction in the CMV+ group than the CMV- group, though this difference was not statistically significant (p = 0.06) (Figure 8B). Similarly, AMP levels displayed higher variability in the CMV- group than in the CMV+ group, but the difference was also insignificant (p = 0.19) (Figure 8C). ADP levels exhibited a trend toward more significant variation in the CMV+ group, though this difference did not reach statistical significance (p = 0.11) (Figure 8D).

Figure 3. (A) analysis of adenosine, **(B)** ATP, **(C)** AMP and **(D)** ADP levels in relation to CMV status and exercise exposure.



(A) Adenosine (µM): CMV- group (before 385.70 ± 83.630, after569.25 ± 162.386); CMV+ group (before 442.55 ± 156.739, after44.66 ± 120.077); **(B) ATP (µM)**: CMV- group (before 44.74 ± 16.052, after 37.79

± 14.142); CMV+ group (before 37.29 ± 8.230, after 37.84 ± 13.087); **(C) ADP (µM)**: CMV- group (before 25.22 ± 11.059, after 35.24 ± 17.285); CMV+ group (before 24.91 ± 7.006, after 24.27 ± 13.174); **(D) AMP (µM)**: CMV- group (before 26.59 ± 10.033, after 28.78 ± 8.427); CMV+ group (before 34.99 ± 13.942, after 32.12 ± 11.991).

Lipopolysaccharides

LPS levels showed an interaction between exercise time and CMV status, with increases observed after exercise in both CMV-negative and CMV-positive groups. However, there were no significant differences in LPS levels between these groups in either the pre- or post-exercise phases (Figure 4). Although the CMV-negative group exhibited greater dispersion in percentage values, with some individuals showing more pronounced increases, the CMV-positive group displayed less variation and lower overall percentages. Despite these visual differences, the statistical analysis did not indicate a significant difference between the groups ($p = 0.11$) (Figure 8E).

Figure 4: Changes in lipopolysaccharide (LPS) levels in response to exercise in CMV-positive and CMV-negative groups.

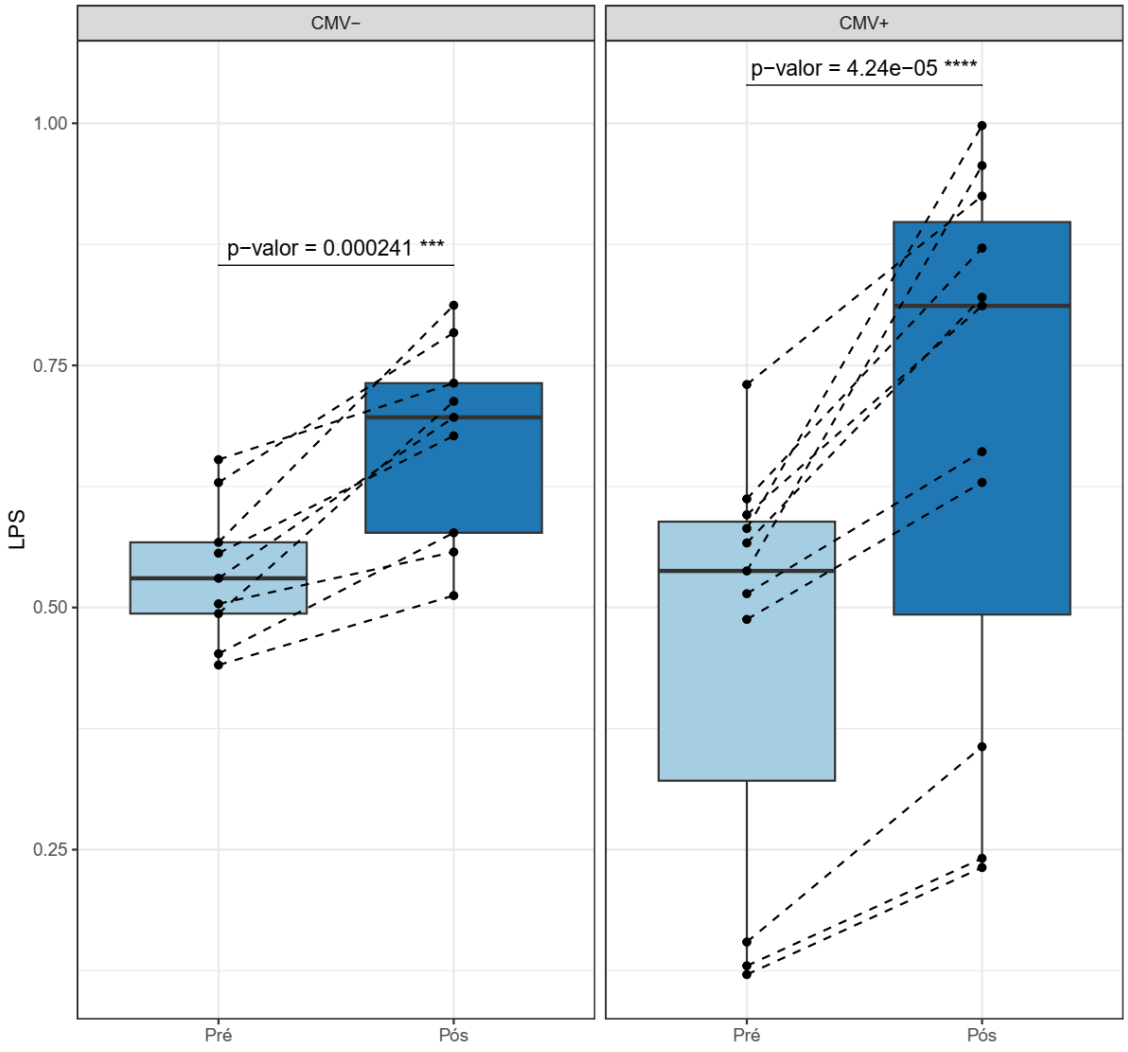


Figure 4. Mean values and standard deviations under different exercise phases, CMV infection status, and LPS levels (μM): CMV- group (before 0.54 ± 0.073, after 0.67 ± 0.103); CMV+ group (before 0.46 ± 0.216, after 0.68 ± 0.285).

Prostaglandin E2

PGE-2 levels showed no interaction between exercise time and CMV group (p-value = 0.821) and no effect of pre- and post-exercise on mean PGE-2 levels (figure 6). However, there was a significant effect of CMV status on mean PGE-2 levels (p-value = 0.026) (figure 5). PGe-2 levels did not differ significantly between the CMV-negative and CMV-positive groups. Both groups exhibited a wide dispersion in percentage values, especially in the CMV-negative group. The mean percentage change was similar between the groups, and the statistical test indicated that the difference was not significant (p = 0.56) (Figure 8F).

Figure 5: Changes in prostaglandin E2 (PGE-2) levels in response to exercise in CMV-positive and CMV-negative groups.

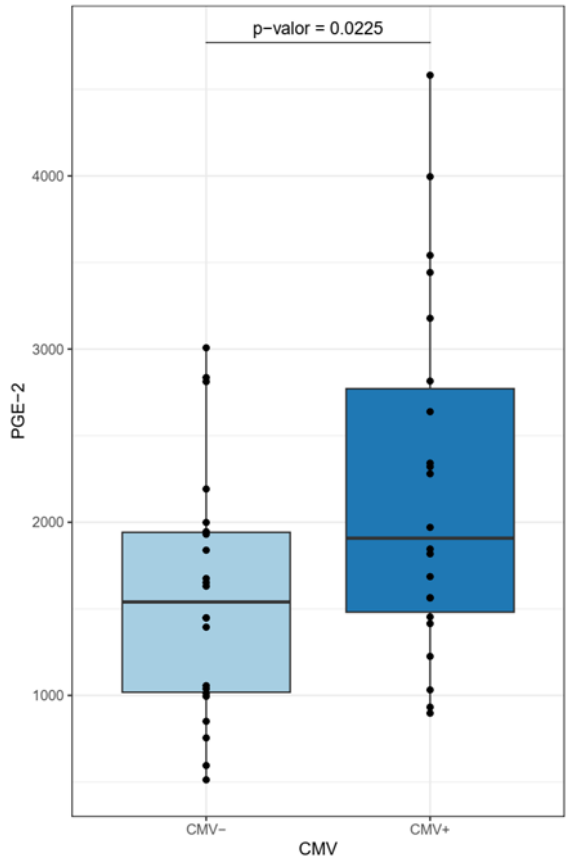


Figure 5. Mean values and standard deviations under different exercise phases and CMV infection status. CMV- group (before 385.70 ± 83.630, after 569.25 ± 162.386); CMV+ group (before 442.55 ± 156.739, after44.66 ± 120.077);

Creatine Kinase

For the CK variable, there was no interaction between exercise time and CMV status (p-value = 0.987) and no effect of CMV condition on mean CK levels (p-value = 0.927). However, there was a significant effect of pre- and post-exercise time on mean CK levels (p-value = 7.53e-06) (Figure 6). The paired t-test indicated a significant increase in mean CK levels following physical exercise (p-value = 4.23e-06). Additionally, both groups showed a wide percentage variation in creatine kinase (CK) levels, but no statistically significant difference was found between them (p = 0.56) (Figure 8G).

Figure 6: Changes in creatine kinase (CK) levels in response to exercise in CMV-positive and CMV-negative groups.

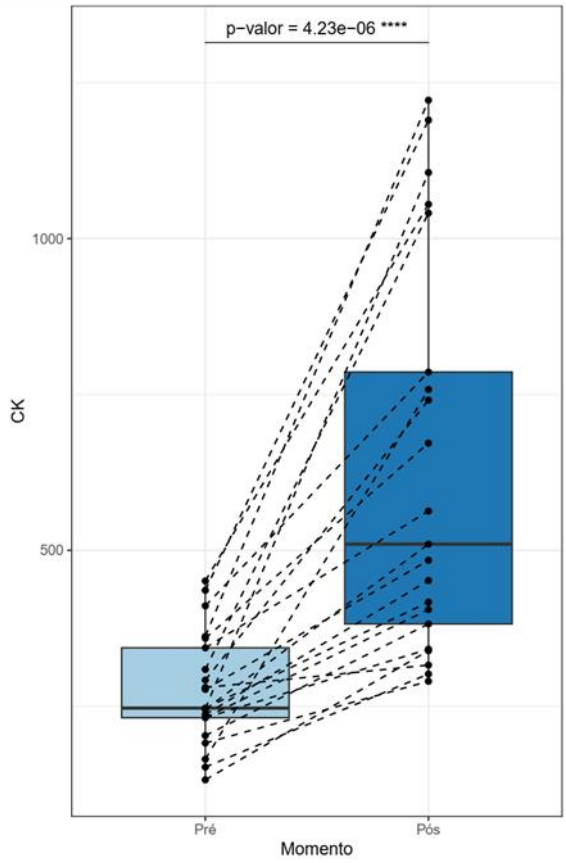


Figure 6. Mean values and standard deviations under different exercise phases and CMV infection status. CMV- group (before 44.74 ± 16.052, after 37.79 ± 14.142); CMV+ group (before 37.29 ± 8.230, after 37.84 ± 13.087).

Interleukine 1-β

For the IL-1β variable, there was an interaction between exercise time and CMV status (p-value = 0.008). The paired t-test indicated a significant increase in mean IL-1β levels after exercise in the CMV+ group (p-value = 0.002) but not in the CMV- group (p-value = 0.327). There were no differences between groups in the pre-exercise phase (p-value = 0.089) but significant differences in the post-exercise phase (p-value = 2.11e-03) (Figure 7). Moreover, the CMV+ group showed a significantly higher percentage variation in IL-1β levels than the CMV- group (p = 0.02). This finding indicates greater inflammatory activation in CMV+ individuals following exercise (Figure 8H).

Figure 7: Changes in Interleukin 1β (IL-1β) levels in response to exercise in CMV-positive and CMV-negative groups.

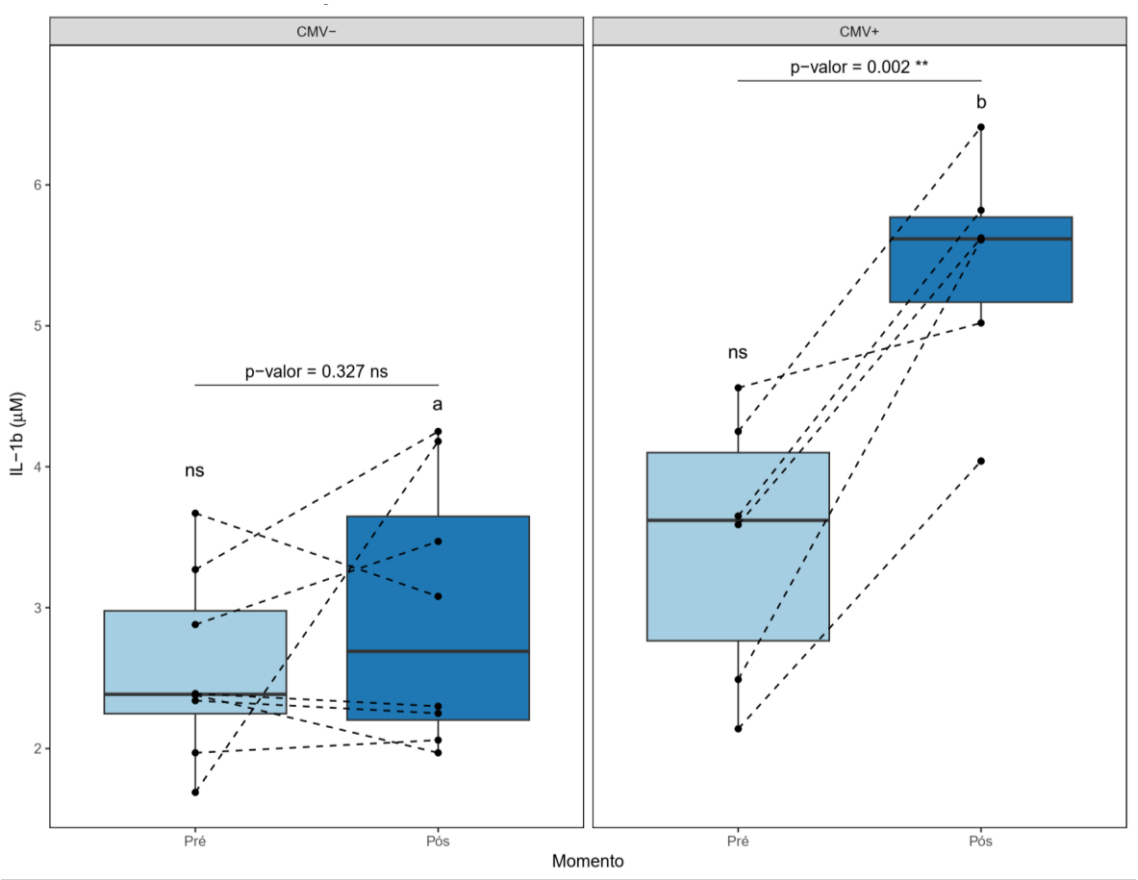
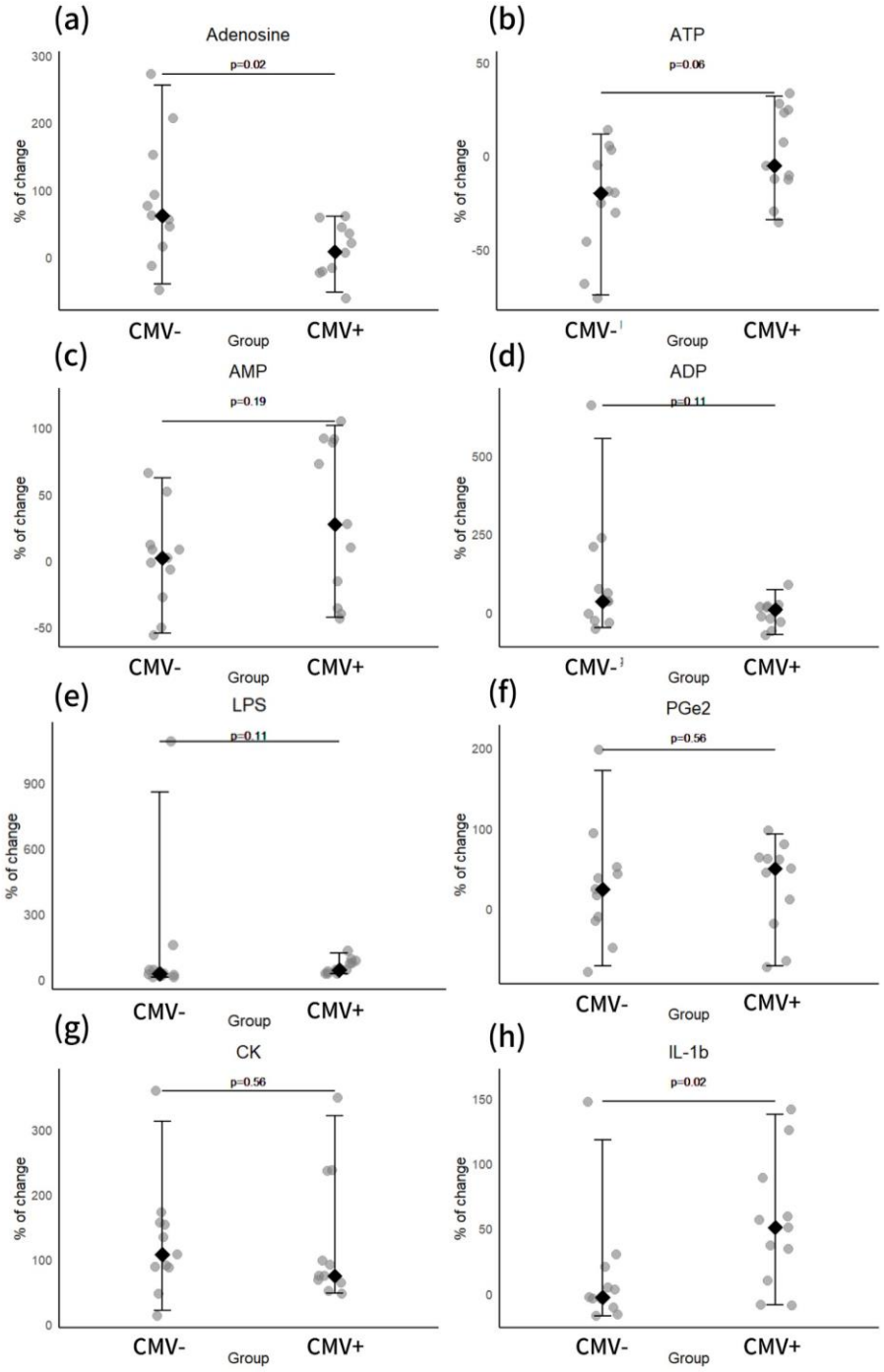


Figure 7. Mean values and standard deviations under different exercise phases, CMV infection status, and IL-1β levels (µM): CMV- group (before 2.57 ± 0.660, after 2.95 ± 0.938); CMV+ group (before 3.45 ± 0.956, after 5.42 ± 0.810).

Figure 8: Analysis of the Dispersion Percentage of Purinergic and Inflammatory Markers in CMV- and CMV+ Individuals After Acute Exercise


(a)
Adenosine
p=0.02
% of change
300
200
100
0
CMV-
CMV+
Group
(b)
ATP
p=0.06
% of change
50
0
-50
CMV-
CMV+
Group
(c)
AMP
p=0.19
% of change
100
50
0
-50
CMV-
CMV+
Group
(d)
ADP
p=0.11
% of change
500
250
0
CMV-
CMV+
Group
(e)
LPS
p=0.11
% of change
900
600
300
0
CMV-
CMV+
Group
(f)
PGe2
p=0.56
% of change
200
100
0
CMV-
CMV+
Group
(g)
CK
p=0.56
% of change
300
200
100
0
CMV-
CMV+
Group
(h)
IL-1b
p=0.02
% of change
150
100
50
0
CMV-
CMV+
Group

342

Figure 8: Percentage changes in the levels of different purinergic, inflammatory, and stress biomarkers after exercise, stratified by CMV status (CMV- and CMV+). The plots show the percentage variation in the levels of (a) adenosine, (b) ATP, (c) AMP, (d) ADP, (e) LPS, (f) PGE2, (g) CK, and (h) IL-1β. CMV status significantly influenced adenosine ($p = 0.02$), ATP ($p = 0.05$), ADP ($p = 0.11$), and IL-1β ($p = 0.02$) levels, with significant increases in CMV+ individuals. LPS, PGE2, AMP, and CK did not show significant differences between CMV- and CMV+ groups. Values are expressed as mean ± SD.

Discussion

The present study investigated the status of CMV in modulating the inflammatory response to exercise.

No significant interactions were found between exercise and CMV status in adenosine, ATP, AMP, and ADP. The absence of significant differences may suggest that purinergic metabolism, represented by the levels of these nucleotides, is not strongly influenced by the presence of CMV during acute exercise, despite high variability between subjects observed pre- and post-exercise.

To date, the literature suggests that high-intensity interval training significantly influences ATP, ADP, AMP, and adenosine levels. Yang et al. demonstrated that HIIT increases ATP concentrations in the myocardial tissues of rats, enhancing their metabolic efficiency (23). Additionally, the acute energy expenditure during HIIT leads to a transient increase in ATP and a corresponding decrease in ADP and AMP levels, reflecting an increase in energy turnover. However, this process is interrupted under hypoxic conditions, resulting in a decrease in mitochondrial ATP production. This reduction is, in turn, directly related to the depletion of phosphoinositides (PI4P and PIP2) in the plasma membrane, disrupting the targeting of proteins (23). On the other hand, increased expression of ectonucleotidases CD39 and CD73, which are responsible for dephosphorylating ATP into adenosine, on CD4+ T cells of highly physically active men may be linked to lower levels of purine nucleosides in the peripheral blood, and acute exercise may have less impact on purines due to increased baseline purinergic enzyme activity compared to non-physical active subjects. In this line, despite differences in the baseline, acute high-intensity exercise induces similar increases in CD39+ and CD73+ expression in high and low-physical-fitness men.

This type of physiological stress significantly alters purine metabolism, affecting cellular energy homeostasis and signaling pathways. Studies have shown that hypoxia

reduces the activity of key enzymes such as inosine monophosphate dehydrogenase (IMPDH) and 5'-nucleotidase (5NT) (24, 25). In human endothelial cells, hypoxia activates purine salvage mechanisms, increasing the degradation of ATP to adenosine (26).

The absence of differences between the interactions may be attributed to several factors. Individuals with chronic infection may have developed metabolic adaptations that mitigate the impact of the virus on energy metabolism. CMV infection significantly alters cellular metabolism, promoting increased glucose uptake and glycolysis to support viral replication (27). In this context, the restriction factor IFI16 is crucial in limiting the metabolic changes induced by CMV by negatively regulating the glucose transporter GLUT4, thereby reducing glucose consumption and lipid synthesis, which may help preserve cellular metabolism (28).

LPS is a molecule found in the outer membrane of gram-negative bacteria. It plays an essential role in the structural integrity of the bacterium and protection against chemical substances. When released into the human body, it can trigger a robust immune response associated with inflammatory processes. Lira et al. demonstrated that plasma LPS concentration is inversely proportional to an individual's level of physical activity (29). The relationship between exercise and LPS levels in CMV individuals is complex and not fully elucidated in the literature. Turner et al. showed that exercise significantly increases the mobilization of CD8 T lymphocytes in CMV+ individuals (30). Lavoy et al. examined the acute immune response in cycling athletes who pedaled 75 km on a mountainous course. Blood samples were analyzed before, after, and 1 hour post-exercise. Although exercise affects immune cell counts, it does not consistently alter LPS levels in CMV+ individuals (31). Similar to the present study, antibodies to CMV did not impact the circulating LPS concentration, and both groups showed an increase in LPS following exercise.

Prostaglandin E2 is an inflammatory mediator, and the elevation of its levels in CMV+ individuals suggests a baseline inflammatory predisposition in these individuals, which may have implications for chronic inflammatory diseases. The interaction between PGE-2 and cytomegalovirus is crucial for viral replication, primarily through the induction of cyclooxygenase-2 (COX-2) (32). CMV infection leads to the positive regulation of COX-2, influencing viral replication in infected cells, including human

retinal epithelial cells and fibroblasts (33). Infection of human fibroblasts with human cytomegalovirus transiently induces COX-2 and increases the production of prostaglandin E2, which is essential for efficient viral replication. COX-2 inhibitors block this production and significantly reduce viral yield, while the addition of prostaglandin E2 can restore infectious yield (33, 34).

Furthermore, PGE-2 modulates immune responses, influencing cytokine expression and impairing the function of cytotoxic lymphocytes, which are crucial for controlling viral infections by positively regulating inhibitory receptors such as PD-1 (34). Modulating PGE-2 signaling pathways may present a promising therapeutic strategy for managing CMV infections. Studies indicate that HCMV manipulates host cell signaling to establish latency and reactivation, suggesting that targeting these pathways may disrupt viral persistence (36). Although the modulation of PGE-2 pathways is promising, the complexity of virus-host interactions necessitates further research for a complete understanding.

Three cytoplasmic isoforms of creatine kinase have been described: CK-MM, CK-MB, and CK-BB. CK-MM is located in various regions of muscle fibers, primarily in areas where ATP consumption is high. A fraction of CK-MM (5-10%) is bound to the M-line structure of myofibrils and serves as a biomarker for myopathies, exercise-induced muscle damage, and energy metabolism, reflecting the intensity of physical activity (36). The relationship between creatine kinase levels and physical exercise is well documented in the literature, with variations observed in different types and intensities of exercise. Intense exercises correlate with increased CK concentrations (37). This is justified by the damage caused to the sarcomeres, resulting in increased membrane permeability. The greater permeability allows CK to leak into the interstitial fluid, which enters the circulation via the lymphatic system (36, 38, 39, 40). Callegari et al. (2017) found that an aerobic exercise protocol at 80% VO2Max resulted in a more significant CK elevation than lower intensity or resistance training protocols (41). Other studies have demonstrated that a HIIT protocol significantly increases CK levels, indicating muscle damage due to training intensity (42, 43). The absence of a significant difference between the CMV+ and CMV- groups suggests that CMV infection does not amplify exercise-induced muscle damage.

There was a significant interaction between exercise timing and CMV condition, with a significant increase in IL-1β levels after exercise in CMV+ individuals. Interleukin 1 beta is a pro-inflammatory cytokine, and its elevation in CMV+ individuals after exercise may indicate an exacerbated inflammatory response, consistent with the literature suggesting that latent infections can exacerbate acute inflammatory responses.

Although exercise generally promotes anti-inflammatory effects, chronic conditions can modulate the IL-1β response. This occurs because CMV infection activates the NLRP3 inflammasome, leading to increased production of IL-1β. This process involves mitochondrial dysfunction and the release of mitochondrial DNA (mtDNA) into the cytosol, triggering inflammatory responses (44). Additionally, CMV alters the composition of memory T cells, increasing the mobilization of CD8+ T cells during exercise, which may influence the overall inflammatory response, including IL-1β levels (45). While CMV infection enhances specific immune responses, it can also lead to T cell exhaustion and immunosenescence, complicating the overall immune landscape during exercise (46).

Regular physical activity seems to mitigate the chronic inflammatory effects associated with CMV, potentially leading to better immune responses and cytokine regulation (47, 48). Studies have linked functional and phenotypic changes in lymphocytes and Natural Killer cells of athletes and more active individuals with seropositivity for CMV (49, 50).

Other chronic conditions directly impact the immune response to physical exercise. Obesity is associated with chronic low-grade inflammation due to the constant activation of adipose tissue, resulting in elevated baseline levels of IL-1β. Acute exercise in obese individuals may increase IL-1β levels post-exercise, indicating an exacerbated inflammatory response due to chronic low-grade inflammation.

Conclusion

The results indicate that CMV infection modulates the inflammatory response to exercise by increasing IL-1β levels in CMV+ individuals (51). In contrast, other inflammatory and purinergic markers showed homogeneous responses between the groups, suggesting a specific impact of CMV on certain inflammatory parameters (51).

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3. CONCLUSÃO GERAL

A conclusão geral do estudo é que a infecção pelo citomegalovírus (CMV) não tem um impacto significativo na metabolização de purinas e na resposta inflamatória durante o exercício físico agudo, apesar de observações de variabilidade individual. Embora a literatura mostre que o treinamento intervalado de alta intensidade (HIIT) possa afetar os níveis de ATP e outras purinas, os resultados sugerem que adaptações metabólicas em indivíduos com infecção crônica podem atenuar essa influência. No entanto, a presença de CMV está associada a um aumento nas respostas inflamatórias, evidenciado pelo aumento de IL-1β após o exercício, indicando que a infecção pode exacerbar as respostas inflamatórias em contextos de atividade física. A prática regular de exercícios pode oferecer benefícios ao moderar os efeitos inflamatórios crônicos associados à infecção por CMV, destacando a complexidade da interação entre exercício, infecção viral e resposta imunológica.

4. IMPACTOS DO TRABALHO

O impacto deste trabalho reside em sua contribuição para a compreensão das interações entre a infecção por citomegalovírus (CMV) e a resposta inflamatória ao exercício físico, revelando que, embora a metabolização de purinas não seja significativamente afetada, a presença do CMV pode exacerbar a produção de citocinas inflamatórias como a IL-1β. Esses achados são fundamentais para profissionais de saúde e treinadores, pois permitem a adaptação de programas de exercícios para indivíduos com infecções crônicas, promovendo intervenções mais eficazes e personalizadas. Além disso, o estudo abre caminhos para pesquisas futuras sobre os mecanismos subjacentes a essas interações e suas implicações na saúde e no desempenho físico.