Universidade de São Paulo

Faculdade de Saúde Pública

Aspectos relacionados à sarcopenia em pessoas vivendo com o vírus da imunodeficiência humana

Marcus Vinicius Lucio dos Santos Quaresma

Tese apresentada para defesa pública ao Programa de Pós-Graduação em Saúde Pública para obtenção do título de Doutor em Ciências.

Área de concentração: Nutrição em Saúde Pública

Orientadora: Prof. Drª. Sandra Maria Lima Ribeiro

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Dedicatória

Nada, absolutamente nada que compõe esta tese foi mais difícil de escrever do que esta seção.

Dedico esta tese a todas as pessoas que morreram por causas associadas a qualquer vírus. Especialmente o HIV e, mais recentemente, o SARS-CoV-2.

Dentre estas pessoas, enalteço o meu Pai, o Sr. Juarez, que não poderei abraçar nunca mais. Que ao longo desta árdua e, frequentemente, injusta trajetória, se foi. O meu Pai não pôde estudar, não teve nenhuma oportunidade. Aqui estou eu, candidato a receber um dos mais importantes títulos acadêmicos, mas que me ceifou incontáveis horas ao lado dele. Um paradoxo. Sorte a minha, se pudesse voltar atrás e optar pela pesca, pelo jogo de futebol, pelo dominó, pela conversa fiada, por qualquer momento ao lado dele, em detrimento da pesquisa. Pai, perdão. Nesta madrugada fria, em que escrevo este texto, só queria o abraço quente do meu iletrado, humilde, querido e eterno amado Pai, o Sr. Juarez.

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RESUMO

QUARESMA, M. V. L. S. **Fatores relacionados à sarcopenia em pessoas vivendo com o vírus da imunodeficiência humana**. 2022. Tese (Doutorado em Ciências) – Faculdade de Saúde Pública, Universidade de São Paulo, São Paulo, 2022.

As terapias antirretrovirais (TARVs) aumentaram a expectativa de vida de pessoas vivendo com HIV (PVHIV). Contudo, os efeitos residuais do HIV e a toxicidade das TARVs parecem prejudicar a integridade do músculo esquelético (ME), deixando as PVHIV mais suscetíveis à sarcopenia. Assim, os objetivos deste estudo foram: (i) compreender os mecanismos fisiopatológicos que explicam o motivo pelo qual PVHIV são mais suscetíveis à sarcopenia; (ii) rastrear entre as PVHIV e que não vivem com HIV (PNVHIV) a prevalência de estar sob risco de sarcopenia, a qualidade de vida relacionada à sarcopenia e os fatores associados; (iii) verificar a prevalência de sarcopenia e dinapenia entre as PVHIV, comparar os componentes da sarcopenia em relação às PNVHIV e verificar os fatores associados aos componentes da sarcopenia; (iv) identificar na literatura científica os estudos que avaliaram o efeito de intervenções nutricionais sobre os parâmetros relacionados ao ME de PVHIV. Assim, quatro artigos foram redigidos para responder cada um dos objetivos descritos acima, incluindo uma revisão narrativa (RN), dois estudos transversais e uma revisão sistemática (RS). Para a RN, estudos pré-clínicos e clínicos foram identificados no MEDLINE/PubMed utilizando as palavras-chave "HIV", "Sarcopenia" e "Antirretrovirais". Nos estudos de delineamento transversal, foram avaliadas PVHIV atendidas no Serviço de Extensão ao Atendimento de Pacientes HIV/AIDS que foram comparadas às PNVHIV. No inquérito virtual foram aplicados o SARC-F e o SarQoL® para identificar a prevalência de estar sob risco de sarcopenia (≥ 4 pontos) e a qualidade de vida relacionada à sarcopenia (abaixo da mediana do escore geral), respectivamente. No estudo presencial foram avaliados a força de preensão manual (FPM), o índice de massa magra apendicular (IMMA), a velocidade de marcha (VM) e os fatores associados à sarcopenia. Em seguida, foi comparada a prevalência de sarcopenia, dinapenia e obesidade dinapênica entre as PVHIV e PNVHIV. Ambos os estudos foram compostos por homens e mulheres com idade ≥18 anos, residentes no estado de São Paulo. Finalmente, a RS foi registrada no prospero CRD42019139981 e seguiu os critérios PICOS para condução da busca. Os dados da RN revelaram que fatores como a inflamação sistêmica, desordens metabólicas e disfunção mitocondrial proveniente das TARVs aumentam a chance de PVHIV desenvolverem sarcopenia. O inquérito virtual (n= 344; 45,5±13,1 anos; 211 PVHIV) revelou que 10,43% (95 % IC: 6,6 – 15,4%) e 0,75% (95% IC: 1,90e-4 – 4%) das PVHIV e PNVHIV estão sob risco de sarcopenia, respectivamente. Similar, PVHIV apresentam pior qualidade de vida relacionada à sarcopenia e os problemas com o sono (OR 7,343; 95 % IC: 3,261 – 16,536; p< 0,001) e a obesidade (OR 4.945; 95% IC: 1,597 – 15,304; p= 0.006) são os principais fatores positivamente associados, ao passo que a prática regular de exercícios físicos está associada a melhor qualidade de vida relacionada à sarcopenia (OR 0.173; 95% IC: 0,080 – 0,375; p< 0,001). O estudo presencial (n= 70; 45,5±7,73 anos; n= 35 PVHIV) revelou que PVHIV e PNVHIV não atenderam os critérios para sarcopenia; entretanto, as PVHIV apresentaram menor FPM (-6,68 kg; p= 0,005) comparativamente às PNVHIV. Ainda, a razão massa gorda: massa magra foi o principal fator associado à menor FPM (ß= -15,476; p< 0,001). O IMMA não diferiu entre os grupos (-0,138 kg/m^2; p= 0,641). Finalmente, na RS, nenhuma intervenção nutricional proposta entre os estudos promoveu aumento da massa muscular em PVHIV.

Descritores: HIV. Antirretrovirais. Sarcopenia. Força Muscular. Músculo Esquelético.

ABSTRACT

QUARESMA, M. V. L. S. **Sarcopenia-relate factors in people living with human immunodeficiency virus**. 2022. Tese (Doutorado em Ciências) – Faculdade de Saúde Pública, Universidade de São Paulo, São Paulo, 2022.

Antiretroviral therapies (ARTs) have increased the life expectancy of people living with HIV (PLWH). However, residual effects of HIV and toxicity from ARTs appear to impair skeletal muscle (SkM) integrity, leaving PLWH more susceptible to sarcopenia. Thus, this study's purpose was: to comprehend the pathophysiological mechanisms that explain why PLWH are more susceptible to sarcopenia; (ii) to verify among PLWH and not living with HIV (PNLWH) the prevalence of living at risk of sarcopenia, sarcopenia-related quality of life, and associated factors; (iii) to verify the prevalence of sarcopenia and dynapenia among PLWH, to compare the components of sarcopenia with PNVHIV and to verify the factors associated with the features of sarcopenia; (iv) to identify the studies that evaluated the effect of nutritional interventions on the SkM-related parameters. Thus, four articles were written to answer each of the purposes, including one narrative review (NR), two cross-sectional studies, and one systematic review (SR). For the NR, preclinical and clinical studies were identified in MEDLINE/PubMed using the keywords "HIV," "Sarcopenia," and "Antiretrovirals." In the cross-sectional design studies, PLWH was evaluated and compared to PNLWH. In the web-based survey, SARC-F and SarQoL® were applied to identify at risk of sarcopenia (≥ 4 points) prevalence and lower sarcopenia-related quality of life (below overall score median), respectively. In the second study, handgrip strength (HGS), appendicular lean mass index (ApLMI), walking speed (WS), and factors associated with sarcopenia were evaluated. Consequently, the prevalence of sarcopenia, dynapenia, and dynapenic obesity among PLWH and PNLWH was compared. Both studies were composed of men and women aged ≥18 years, residing in the state of São Paulo. Finally, the SR was registered in the PROSPERO CRD42019139981 and followed the PICOS criteria for searching. The data from the NR revealed that factors such as systemic inflammation, metabolic disorders, and mitochondrial dysfunction arising from ARTs increase the odds of PLWH being sarcopenic. The web-based survey (n= 344; 45.5±13.1 years; 211 PLHIV) revealed that 10.43% (95% CI: 6.6 - 15.4%) and 0.75% (95% CI: 1.90e-4 - 4%) of PLWH and PNLWH are at risk of sarcopenia, respectively. Similar, PLWH have worse sarcopenia-related quality of life and sleep problems (OR 7.343; 95% CI: 3.261 - 16.536; p< 0.001) and obesity (OR 4.945; 95% CI: 1.597 - 15.304; p= 0.006) are the main positively associated factors, whereas regular exercise is associated with lower odds to poor sarcopenia-related quality of life (OR 0.173; 95% CI: 0.080 - 0.375; p< 0.001). The second transversal study (n= 70; 45.5±7.73 years; n= 35 PLHIV) revealed that PLWH and PNLWH did not meet criteria for sarcopenia; however, PLWH had lower HGS (-6.68 kg; p= 0.005) compared to PNLWH. Also, the fat mass: lean mass ratio was the main factor associated with lower HGS (ß= -15.476; p< 0.001). ApLMI did not differ between groups (-0.138 kg/m^2; p= 0.641). Finally, no nutritional intervention in SR promoted increased muscle mass in PLWH.
Keywords: HIV. Antiretroviral. Sarcopenia. Muscle strength. Skeletal muscle.

Lista de Figuras

Figura 1. Vírus da imunodeficiência humana e os seus componentes.
Figura 2. Ciclo de replicação do vírus da imunodeficiência humana.
Figura 3. Etapas de atuação dos antirretrovirais no processo de replicação do vírus da imunodeficiência humana.
Figura 4. Alterações intestinais como mediadora da imunoativação persistente em PVHIV.
Figura 5. Via inflamatória mediada pelo LPS.
Figura 6. Tecido adiposo e inflamação sistêmica.
Figura 7. Vias moleculares responsáveis pelo balanço proteico muscular.
Figura 8. Mediadores inflamatórios que afetam o estado muscular.
Figura 9. Algoritmo de sarcopenia segundo o EWGSOP.

Lista de Quadros e Tabelas

Quadro 1. Classe, medicamentos e ano de publicação das terapias antirretrovirais.

Quadro 2. Similaridades entre PVHIV e idosos no que tange a imunossenescência.

Lista de Abreviaturas

3TC = Lamivudina
4EBP1 = eukaryotic translation initiation factor 4E binding protein 1
AGCCs = ácidos graxos de cadeia curta
AGL = ácidos graxos livres
AIDS/SIDA = Síndrome da Imunodeficiência Humana Adquirida
Akt = proteína quinase B
APCs = células apresentadoras de antígenos
ATP = adenosina trifosfato
AZT = Zidovudina
C/EBPα = CCAAT/enhancer binding protein alpha
CCR2 = C-C chemokine receptor type 2
CCR5 = C-C receptor de quimiocina do tipo 5
CD = cluster of differenciation ou grupo de diferenciação
CEI = células epiteliais intestinais
COM = catabolismo proteico muscular
CTE = cadeia de transporte de elétrons
CX3CR1 = CX3C chemokine receptor 1
CXCR4 = receptor de quimiocina do tipo 4
DAMPs = padrões moleculares associados a danos
DC = células dendríticas
DEXA = absorciometria por raios-X com dupla energia
DNA = ácido desoxirribonucleico
DTG = dolutegravir
EROs = espécies reativas ao oxigênio
fDC = células dendríticas foliculares
FPM = força de preensão manual
FPP = força de preensão palmar
GALT = tecido linfoide associado ao intestino
GALT = tecido linfoide associado ao intestino GALT
GLUT-4 = transportador de glicose do tipo 4
GP = glicoproteína

GPR = G-protein coupled receptor

HAART = Highly Active Antiretroviral Therapy

HIV = Vírus da Imunodeficiência Humana

HLA-DR = major histocompatibility complex, class II, DR alpha

HMGB1 = high-mobility group box

IκB quinase = I-kappa-B-kinase

IκBα = inhibitor of nuclear factor kappa B

IF = inibidores de fusão

IFABP = intestinal fatty acid biding protein

IGF-1 = fator de crescimento semelhante à insulina 1

IKK quinase = I-kappa-kinase

IL = interleucina

IMC = Índice de Massa Corporal

IMMA = Índice de Massa Muscular Apendicular

INI = inibidores da integrasse

INNTR = não nucleosídicos da transcriptase reversa

INTR = inibidores nucleosí(tí)dicos da transcriptase reversa

IP = inibidores de protease

IRAK-4 = IL-1 receptor-associated kinase-4

IRF-7 = Interferon regulatory factor 7

IRS-1 = substrato do receptor de insulina 1

ISBG = inflamação sistêmica de baixo grau

LPB = proteína de ligação a lipopolissacarídeo

LPL = lipase lipoproteica

LPS = lipopolissacarídeo

MCP-1 = proteína de quimiotaxia de monócitos 1

mDC = células dendríticas mieloides

ME = músculo esquelético

MI = microbiota intestinal

MM = massa muscular

MMA = massa muscular apendicular

mTOR = mecanismo alvo da rapamicina

MyD88 = a myeloid differentiation primary response gene 88

Nef = negative factor

NF-κB = fator nuclear kappa B

NK = células natural killer

NLR = NOD-like receptor

NLRP3 = NLR family pyrin domain containing 3

p70S6K1 = p70 ribosomal S6 kinase 1

PAMPs = padrões moleculares associados a patógenos

PCR = proteína C reativa

pDC = células dendríticas plasmocitoides

PI3K = proteína fosfoinositol-3 quinase

PKB = proteína quinase B

PPARγ = peroxisome proliferator-activated receptors gamma

PVHIV = pessoas vivendo com HIV

RLR = RIG-like receptor

RNA = ácido ribonucleico

sCD = soluble cluster of differenciation ou grupo de diferenciação solúvel

sICAM-1 = soluble intercellular adhesion molecule 1

SIV = Vírus da Imunodeficiência Símia

SPM = síntese proteica muscular

SREBP1 = Sterol regulatory element binding protein 1

TA = tecido adiposo

TAK1 = transforming growth factor-β-activated kinase

TARVs = Terapias antirretrovirais

Tat = transactivator of transcription

TDF = Tenofovir

TIR = toll-interleukin-1 receptor

TLR = toll-like receptor

TNF-α = fator de necrose tumoral alfa

TRAF6 = TNF receptor-associated factor 6

UNAIDS = Programa Conjunto das Nações Unidas sobre HIV/AIDS

Vif = virion infectivity factor

Vpr = viral protein R

Vpu = viral protein U

SUMÁRIO

1 INTRODUÇÃO 16

1.1 REVISÃO DE LITERATURA 19

1.1.1 HIV e AIDS: Dados epidemiológicos 19
1.1.2 Vírus da imunodeficiência humana 21
1.1.3 Terapia antirretroviral 23
1.1.4 HIV, TARVs, imunoativação persistente e inflamação sistêmica de baixo grau 29
1.1.5 Similaridades entre o envelhecimento e as PVHIV 37
1.1.6 Inflamação sistêmica como fator etiológico para sarcopenia em PVHIV 48
1.1.7 Avaliação da sarcopenia e sarcopenia em pessoas vivendo com HIV 52
1.1.8 Sarcopenia em pessoas vivendo com HIV 58
1.1.9 Estratégias nutricionais baseadas em proteínas e aminoácidos isolados para manutenção ou aumento dos parâmetros musculares relacionados à sarcopenia 59

2 JUSTIFICATIVA 62

3 HIPÓTESES 63

4 OBJETIVOS 64

4.1 Objetivo geral: 64

4.2 Objetivos específicos: 64

5 MÉTODOS 66

5.1 Estudo 1 - Persons Living with HIV under Antiretroviral Therapy: A Literature Review 66

5.2 Estudo 2 - Sarcopenia risk, sarcopenia-related quality of life, and associated factors in people living with human immunodeficiency virus (HIV): a web-based survey 67

5.3 Estudo 3 - Sarcopenia in people living with HIV and associated factors: a cross-sectional study. 73

5.4 Estudo 4 - Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in persons living with HIV (PLWH): a systematic review 82

6 RESULTADOS 85

6.1 Artigo 1 – Sarcopenia in Persons Living with HIV under Antiretroviral Therapy: A Literature Review 86

6.2 Artigo 2 – Sarcopenia risk and sarcopenia-related quality of life, and associated factors in people living with human immunodeficiency virus (HIV): a web-based survey 101

6.3 Artigo 3 – Sarcopenia in people living with HIV and associated factors: a cross-sectional study 132

6.4 Artigo 4 – Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in people living with HIV (PLWH): a systematic review 163

7 CONCLUSÃO E CONSIDERAÇÕES FINAIS 208

8 REFERÊNCIAS 210

APÊNDICES 238

Apêndice A – Questionário utilizado para coleta de dados da pesquisa online 238

ANEXOS 247

ANEXO A - PARECER CONSUBSTANCIADO DO CEP – Projeto Rastreio de sarcopenia, alterações cognitivas e relações com estilo de vida em pessoas vivendo com o vírus da imunodeficiência humana em terapia antirretroviral: um estudo transversal. 247

ANEXO B – Questionário de rastreio de sarcopenia - SARC - F 250

ANEXO C – Questionário de qualidade de vida associado a sarcopenia - SarQoL® 251

ANEXO D - Mini Sleep Questionnaire (MSQ) 257

ANEXO E - PARECER CONSUBSTANCIADO DO CEP – Dieta, inflamação sistêmica e desfechos à saúde em pessoas que vivem com o vírus HIV em terapia antirretroviral: rastreio inicial para planejamento de um estudo clínico. 258

CURRÍCULO LATTES 261

Artigos científicos e capítulos de livros produzidos em colaboração ao longo do doutorado 266

Artigo 1 – The dietary inflammatory index (DII®) and its association with cognition, frailty, and risk of disabilities in older adults: A systematic review – Publicado na Clinical Nutrition ESPEN (Clin Nutr ESPEN. 2020 Dec;40:7-16.) 267

Artigo 2 – Dietary patterns and sleep quality in young adults: a systematic review. Submetido à revista Sleep Health e negado. Atualmente está em ajuste para nova submissão 277

Artigo 3 – Covid-19 social distancing, lifestyle and health outcomes among Persons living with HIV (PLWH): a web-based survey – Artigo publicado na AIDS and Behavior.....309

Artigo 4 - Association between sleep quality and lifestyle factors in persons living with HIV during the COVID-19 social distancing: a web-based survey. Submetido à revista Sleep Health e negado. Atualmente está em ajuste para nova submissão.....321

Capítulo de Livro – Modificações da Microbiota Intestinal e Associação com Inflamação Sistêmica do Envelhecimento. Publicado – Programa de Atualização em Nutrição Clínica: Ciclo 10 / Organizado pela Associação Brasileira de Nutrição.....335

Outras atividades acadêmicas relacionadas ao Doutorado 359

International Conference on Frailty & Sarcopenia Research.....359

International Conference on Cachexia, Sarcopenia & Muscle Wasting 360

XIV Curso Avançado de Patogênese do HIV.....361

1 INTRODUÇÃO

O vírus da imunodeficiência humana (HIV) é o causador da Síndrome da Imunodeficiência Humana Adquirida (SIDA, ou AIDS) e considerado um dos vírus mais estudados nos últimos 40 nos (FARIA; RAMBAUT; SUCHARD; BAELE *et al.*, 2014).

Na década de 1980, no início da epidemia, diversas pessoas morreram por causas associadas à AIDS, especialmente, pela ausência de tratamentos eficientes. Todavia, com o advento e o aperfeiçoamento das terapias antirretrovirais (TARVs) foi possível controlar a replicação do HIV, o que permitiu a redução significativa de mortes ao longo das últimas décadas (ANDEREGG; JOHNSON; ZANIEWSKI; ALTHOFF *et al.*, 2017; FRANK; CARTER; JAHAGIRDAR *et al*., 2019). Dados provenientes da UNAIDS (2021) mostraram que 37,7 (95% IC: 30,2 – 45,1) milhões de pessoas estimadas vivem atualmente com HIV no mundo, e a incidência de infectados em 2020 foi de 1,5 milhão, ao passo que somente 680 mil pessoas morreram de causas relacionadas ao HIV (UNAIDS, 2021).

As TARVs, portanto, proporcionaram um novo cenário epidemiológico, com maior expectativa de vida para pessoas vivendo com HIV (PVHIV). No mundo, em 2016, 5,7 milhões de pessoas com idade ≥ a 50 anos viviam com HIV, número três vezes maior comparativamente ao ano 2000. Em 2020, esse número se elevou para aproximadamente 7,5 milhões de pessoas (AUTENRIETH; BECK; STELZLE; MALLOURIS *et al.*, 2018).

A maior sobrevida das PVHIV é uma conquista indiscutível da ciência. Porém, este novo cenário epidemiológico trouxe a necessidade de discussões sobre os aspectos relacionados à saúde e à qualidade de vida das pessoas envelhecendo com HIV. Embora as TARVs sejam indispensáveis para a sobrevida das PVHIV, alguns estudos mostraram que os esquemas terapêuticos não são capazes de restaurar por completo o sistema imunológico como, por exemplo, recuperar totalmente os linfócitos T $CD4^+$ (WILSON; SERETI, 2013). Ainda, os mecanismos de ação das TARVs no processo de inibição da replicação viral podem promover alterações celulares e moleculares permanentes (p. ex., menor adipogênese e maior toxicidade mitocondrial) (KOETHE; LAGATHU; LAKE; DOMINGO *et al.*, 2020). Por conseguinte, acredita-se que mesmo com a carga viral controlada, o HIV e as TARVs são capazes de alterar a função de sistemas, tecidos e células do sistema imunológico. Por exemplo, no intestino, entre as alterações decorridas da redução dos linfócitos T $CD4^+$, inclui-se o aumento da permeabilidade intestinal, que aumenta a translocação de fragmentos bacterianos capazes de

estimular vias inflamatórias locais e sistêmicas (AHMAD; SORRELL; BATRA; DHAWAN *et al.*, 2017).

O tecido adiposo (TA) também é responsivo ao HIV e às TARVs. Proteínas associadas ao vírus, como a Nef e Tat, estimulam a produção de espécies reativas ao oxigênio (EROs), e favorecem a síntese de citocinas inflamatórias, como a interleucina (IL)-6 e o fator de necrose tumoral alfa (TNF-α) (KOETHE; LAGATHU; LAKE; DOMINGO *et al.*, 2020). Além disso, embora os efeitos não sejam similares entre os medicamentos que compõem as TARVs, alguns antirretrovirais promovem alterações metabólicas que incorrem na hipertrofia dos adipócitos e a mudanças no fenótipo das células imunológicas locais, maximizando a produção de IL-6 e TNF-α (KOETHE; LAGATHU; LAKE; DOMINGO *et al.*, 2020). Ademais, os linfócitos T $CD8^+$ permanecem ativados em resposta ao HIV, ampliando a produção e a circulação de citocinas e outros mediadores inflamatórios (HILEMAN; FUNDERBURG, 2017). Comparativamente as pessoas não infectadas, PVHIV em tratamento e com a carga viral controlada, exibem maior ativação de linfócitos T. Em conjunto, estas alterações são favoráveis à instalação de um ambiente inflamatório persistente, reconhecida como inflamação sistêmica de baixo grau (ISBG) (HUNT, 2012).

Este quadro de ISBG é um dos principais pilares para a hipótese da antecipação do envelhecimento fisiológico e celular, bem como do desenvolvimento de diversas doenças não-AIDS entre as PVHIV (DE FRANCESCO; WIT; BURKLE; OEHLKE *et al.*, 2019; ORTA-RESENDIZ; VIVEROS-ROGEL; FUENTES-ROMERO; VERGARA-MENDOZA *et al.*, 2020; TUTTLE; THANG; MAIER, 2020). Dentre estas doenças, inclui-se a sarcopenia, que pode ser definida pela redução da força e da massa muscular, podendo levar ao comprometimento do desempenho físico (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019). Acerca dos fatores etiológicos relacionados à sarcopenia, embora apresentem um importante componente genético, também são amplamente influenciados pelo estilo de vida (p. ex., alimentação, nível de atividade física, padrão de sono, uso de substâncias como álcool e tabaco etc.) (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019). A sarcopenia pode ser categorizada em primária, tendo como principal fator predisponente o envelhecimento, e secundária, que decorre de outras doenças ou condições. Além disso, a inatividade física, proveniente do sedentarismo ou de doenças incapacitantes, bem como a menor ingestão energética e de proteínas alimentares, derivada da anorexia do envelhecimento, de problemas absortivos e da limitação ao acesso ao alimento, fazem parte da matriz de fatores relacionados à sarcopenia secundária (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019).

Levando em consideração que a ISBG parece ser um importante fator para o desenvolvimento da sarcopenia primária e secundária, haja vista que o músculo esquelético (ME) é responsivo a diferentes mediadores inflamatórios, PVHIV são potenciais candidatos ao seu desenvolvimento antecipadamente (BANO; TREVISAN; CARRARO; SOLMI *et al.*, 2017; DALLE; ROSSMEISLOVA; KOPPO, 2017).

Os estudos que avaliaram os aspectos relacionados à sarcopenia em PVHIV são escassos e heterogêneos. Recentemente, Oliveira *et al.* (2020) mostraram que a prevalência de sarcopenia foi de 24% em PVHIV, enquanto a chance de pertencer ao grupo sarcopenia foi de OR 6,1 (95% IC: 1,1 – 33,5) comparativamente as pessoas que não vivem com HIV. Entretanto, estes dados são provenientes de diferentes critérios utilizados para definir sarcopenia. Destaca-se, ainda, que os estudos que se propuseram a avaliar a prevalência de sarcopenia em PVHIV utilizaram, especialmente, apenas a redução de dois desvios padrão da massa muscular apendicular corrigida pela estatura ao quadrado, levando em consideração os critérios estabelecidos pelo consenso Europeu de 2010 (CRUZ-JENTOFT; BAEYENS; BAUER; BOIRIE *et al.*, 2010), que contou com dados provenientes de pessoas com idade média acima de 70 anos e o referencial foi composto por pessoas jovens com idade média menor de 30 anos (GALLAGHER; VISSER; DE MEERSMAN; SEPULVEDA *et al.*, 1997; BAUMGARTNER; KOEHLER; GALLAGHER; ROMERO *et al.*, 1998). O ajustado e mais recente consenso Europeu para definir sarcopenia, publicado em 2019, é mais exigente, isto é, propõe valores menores de força e de massa muscular como critério para discriminar sarcopenia, bem como modificou o algoritmo para definir sarcopenia, elencando a força muscular como principal fator (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019). Contudo, estes consensos não consideraram PVHIV em suas amostras de referência; portanto, seu uso pode oferecer estimativas limitadas e equivocadas acerca da real prevalência de sarcopenia em PVHIV. Em 2020, o consenso americano de sarcopenia incluiu em sua amostra estudos que avaliaram PVHIV para definição dos pontos de corte da força e da massa muscular (BHASIN; TRAVISON; MANINI; PATEL *et al.*, 2020). Entretanto, o recente estudo de Erlandson *et al.* (2020) que considerou os pontos de corte deste novo consenso, demonstrou baixo desempenho (p. ex., baixa sensibilidade e especificidade) dos parâmetros avaliados (p. ex., força de preensão manual e massa muscular) para discriminar importantes alterações inerentes à sarcopenia, como quedas e lentidão motora (ERLANDSON; TRAVISON; ZHU; MAGAZINER *et al.*, 2020). Assim, independente do critério utilizado, com base nos dados disponíveis, o grau de sensibilidade, especificidade e o valor preditivo dos pontos de corte disponíveis nestes

consensos para identificar sarcopenia em PVHIV ainda são limitados e devem ser interpretados com cautela.

Considerando estas lacunas e interpretações limitadas, poucas pesquisas exploraram a suscetibilidade das pessoas vivendo com HIV se tornarem sarcopênicas, bem como não há dados disponíveis sobre a qualidade de vida relacionada à sarcopenia de pessoas vivendo com HIV. Ademais, tendo como base os critérios mais atuais para determinar sarcopenia, pouco se sabe sobre a prevalência desta doença nesta população. Ainda, isoladamente, a força muscular, a qualidade muscular e outros componentes da composição corporal não foram investigados com profundidade nas pessoas vivendo com HIV. Neste sentido, os esquemas de antirretrovirais utilizados atualmente, bem como medicamentos utilizados no início da epidemia do HIV/AIDS, não foram considerados nos estudos que propuseram avaliar os fatores relacionados à sarcopenia nesta população.

Ainda, insuficientes e heterogêneos estudos avaliaram o efeito de intervenções, principalmente nutricionais, sobre o músculo esquelético das PVHIV. Sendo assim, estes dados justificam a necessidade de compreender os fatores associados, avaliar e investigar a respeito de potenciais intervenções nutricionais capazes de mitigar as alterações musculares relacionadas à sarcopenia em PVHIV.

1.1 REVISÃO DE LITERATURA

1.1.1 HIV e AIDS: Dados epidemiológicos

O HIV é o causador da AIDS, uma das doenças mais letais das décadas de 1980 e 1990 (UNAIDS, 2021). A primeira descrição da AIDS ocorreu em 1981 (FANNIN *et al*., 1981) e o isolamento do HIV ocorreu apenas em 1983 (BARRE-SINOUSSI; CHERMANN; REY; NUGEYRE *et al.*, 1983). O HIV é considerado um dos vírus mais estudados nos últimos 40 anos, embora sua transmissão ocorra desde o início do século XX (FARIA; RAMBAUT; SUCHARD; BAELE *et al.*, 2014; SHARP; BAILES; CHAUDHURI; RODENBURG *et al.*, 2001).

Desde o começo da epidemia de HIV, na década de 1980, 79,3 (95% IC: 55,9 – 110) milhões de pessoas já foram infectadas e 36,3 (95% IC: 27,2 – 47,8) milhões já morreram de causas associadas ao HIV/AIDS (UNAIDS, 2021). Atualmente, com base nos dados epidemiológicos provenientes da UNAIDS e publicados em 2021, estima-se que 37,7 (95% IC: 30,2 – 45,1) milhões de pessoas vivam com HIV. Ademais, em 2020, 1,5 (95% IC: 1,0 – 2,0)

milhão de pessoas foram infectadas e 680 mil morreram por causas associadas à AIDS (UNAIDS, 2021). Globalmente, em 2020, das pessoas estimadas, 84% (31,6 milhões) de PVHIV estavam infectadas, 73% (27,4 milhões) tiveram acesso ao tratamento e 66% (24,8 milhões) tiveram suas cargas virais indetectáveis pela utilização da TARV (FRANK; CARTER; JAHAGIRDAR *et al.*, 2019).

Os principais comportamentos e condições que possibilitam aos indivíduos maior risco de contrair o HIV incluem a prática sexual desprotegida, especialmente, com pessoas com a carga viral não controlada, compartilhamento de agulhas, seringas e outros equipamentos de injeção, procedimentos médicos que envolvam cortes e soluções de drogas contaminadas ou sofrer ferimentos acidentais com agulhas, inclusive entre os profissionais de saúde (WORLD HEALTH ORGANIZATION, 2021).

Atualmente, no que se refere às maneiras de infecção pelo HIV, as práticas sexuais desprotegidas, sobretudo, por homens que fazem sexo com homens (p. ex., heterossexuais, bissexuais, homossexuais, ou sem categoria definida) se destacam como principal maneira de infecção pelo HIV, exceto na África, local cuja transmissibilidade é predominantemente proveniente de pessoas heterossexuais (UNAIDS, 2021). Ainda, trabalhadores do sexo e seus clientes, transgêneros e usuários de drogas injetáveis compreendem o grupo chamado de "população chave". Este grupo foi responsável por 65% das novas infecções por HIV no mundo em 2020 (UNAIDS, 2021). Na América Latina, 2,1 milhões de pessoas vivem com HIV e o número de novos infectados foi de aproximadamente 100 mil pessoas em 2020. No mesmo ano, no Brasil, 930 mil (95% IC: 450 mil – 1,4 milhão) pessoas, incluindo crianças e adultos vivem com HIV. A prevalência de HIV no Brasil é de 0,6 % (95% IC: 0,3 – 0,8%), sendo mais prevalente em homens 0,7% (95% IC: 0,3 – 1,1%) comparativamente às mulheres 0,4 (0,2 – 0,6). Em 2020, no Brasil, 48 mil pessoas (95% IC 23 - 70 mil) se infectaram com o HIV e 13 mil (95% IC: 5,2 – 21 mil) morreram de causas associadas à AIDS. Estima-se que 650 mil PVHIV no Brasil estejam utilizando TARVs, aproximadamente 70 % (95% IC: 34 - 98%). Ainda, 620 mil PVHIV no Brasil estão com a carga viral indetectável 66% (95% IC: 32 – 97%). Segundo os dados disponíveis, a prevalência de HIV no Brasil é concentrada na população chave (UNAIDS, 2021).

Apesar desta prevalência de HIV, destaca-se que, globalmente, o número de novos casos reduziu em aproximadamente 52% desde o pico da epidemia no ano de 1997, e desde 2010 o declínio foi de 31% (UNAIDS, 2021).

1.1.2 Vírus da imunodeficiência humana

O HIV pode ser categorizado em HIV-1, mais frequente e virulento, e HIV-2, menos frequente e virulento (NYAMWEYA; HEGEDUS; JAYE; ROWLAND-JONES *et al.*, 2013). Tendo em vista que o HIV-1 é o mais discutido e disseminado, na presente tese será descrito apenas como HIV. O HIV é um retrovírus que contém duas fitas simples de ácido ribonucleico (RNA) viral, proteínas de superfície e transmembanares como as glicoproteínas (GP) 120 e GP41, enzimas como protease, transcriptase reversa e integrase, proteínas acessórias como vif, vpr, vpu e nef e estruturas internas, como o capsídeo e o núcleo capsídeo (**Figura 1**). Estas características fazem do HIV um vírus com elevada capacidade de replicação e permitem que mecanismos sofisticados de "refúgio" sejam ativados, dificultando a inibição do processo de replicação do HIV (MELIKYAN, 2014).

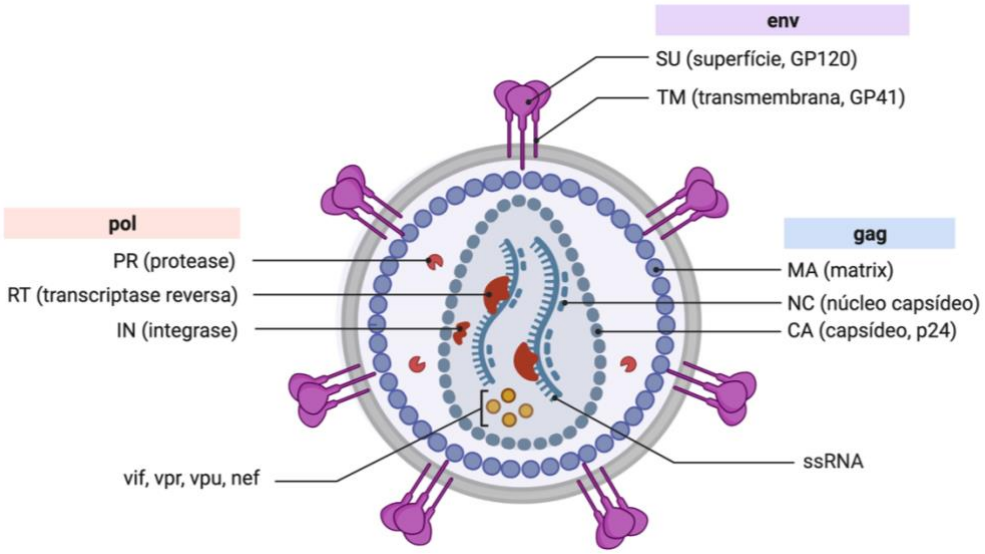

Figura 1. Vírus da Imunodeficiência Humana e os seus componentes. Legenda: gag polyprotein (gag), pol polyprotein (pol), envelop protein (env), virion infectivity factor (vif), viral protein R (vpr), viral protein U (vpu), negative factor (nef). Adaptado e traduzido de ENGELMAN e CHEREPANOV (2012).

O HIV tem como alvo as células do sistema imunológico do hospedeiro que expressam em sua superfície o *cluster of differenciation* ou grupo de diferenciação (CD)4, incluindo linfócitos T, macrófagos e células dendríticas (DC) (CHUN; ENGEL; MIZELL; HALLAHAN *et al.*, 1999; SMITH; GARTNER; LIU; PERELSON *et al.*, 2001; SONZA; MUTIMER; OELRICHS; JARDINE *et al.*, 2001). Os linfócitos T são os principais alvos do HIV e o intestino é considerado o mais importante reservatório de linfócitos T $CD4^+$. Essa maior afinidade do HIV pelos linfócitos T $CD4^+$ intestinais se deve a maior expressão do C-C receptor de quimiocina do tipo 5 (CCR5), um correceptor que desempenha um papel crítico na entrada

do vírus às células. Portanto, o intestino é considerado um local de rápida proliferação do HIV (BRENCHLEY; SCHACKER; RUFF; PRICE *et al.*, 2004; MUDD; BRENCHLEY, 2016).

O processo de replicação do HIV é complexo e ocorre em ao menos nove etapas conforme descrito na **Figura 2**. A entrada do HIV na célula envolve diversas proteínas. Por exemplo, inicialmente, pelo envelope viral via GP120 e GP41, o HIV se liga ao CD4 e ao CCR5 ou C-X-C receptor de quimiocina do tipo 4 (CXCR4). O tropismo pelo CXCR4 é menor e, por isso, células que expressam mais CCR5 são mais infectáveis pelo HIV (PRICE; KEANE; GRAY; LEE *et al.*, 2006). Essa interação possibilita mudanças conformacionais nas glicoproteínas, na estrutura do vírus e na célula invadida, permitindo a aglutinação e a sua entrada, processo reconhecido como endocitose (ENGELMAN; CHEREPANOV, 2012). Em seguida, o capsídeo se rompe e libera o material genômico (RNA) viral no citosol da célula. O RNA, por sua vez, sofre ação da enzima transcriptase reversa para produção do ácido desoxirribonucleico (DNA) viral, que será internalizado no núcleo celular. O DNA viral, por meio da enzima integrase, é unificado ao DNA da célula invadida que, em seguida, após os processos de transcrição e tradução proteica, permitirá a formação de um novo vírus. Após esta etapa, o vírus será montado, isto é, as proteínas (p. ex., vif, nef, vpr, vpu) e as enzimas (p. ex., integrase, transcriptase reversa e protease) que o acompanham serão agregadas ao vírus. O processo segue para a etapa de maturação, na qual, o HIV é direcionado para sair da célula já infectada e invadir outras células do sistema imunológico (ENGELMAN; CHEREPANOV, 2012; GOMEZ; HOPE, 2005).

Destaca-se que o HIV apresenta uma elevada capacidade de mutagenicidade e de ativar mecanismos que dificultam a ação do sistema imunológico do hospedeiro. Além disso, os diversos reservatórios do HIV (p. ex., intestino, tecido adiposo, trato genital, células linfoides e o cérebro) permitem a manutenção da replicação viral (MELIKYAN, 2014; STEIN; STORCKSDIECK GENANNT BONSMANN; STREECK, 2016).

Portanto, levando em consideração que não há uma cura definitiva para o HIV, medicamentos capazes de reduzir a sua replicação foram desenvolvidos e utilizados nas últimas décadas. As TARVs modificaram a trajetória do HIV/AIDS e possibilitaram um novo cenário epidemiológico às PVHIV.

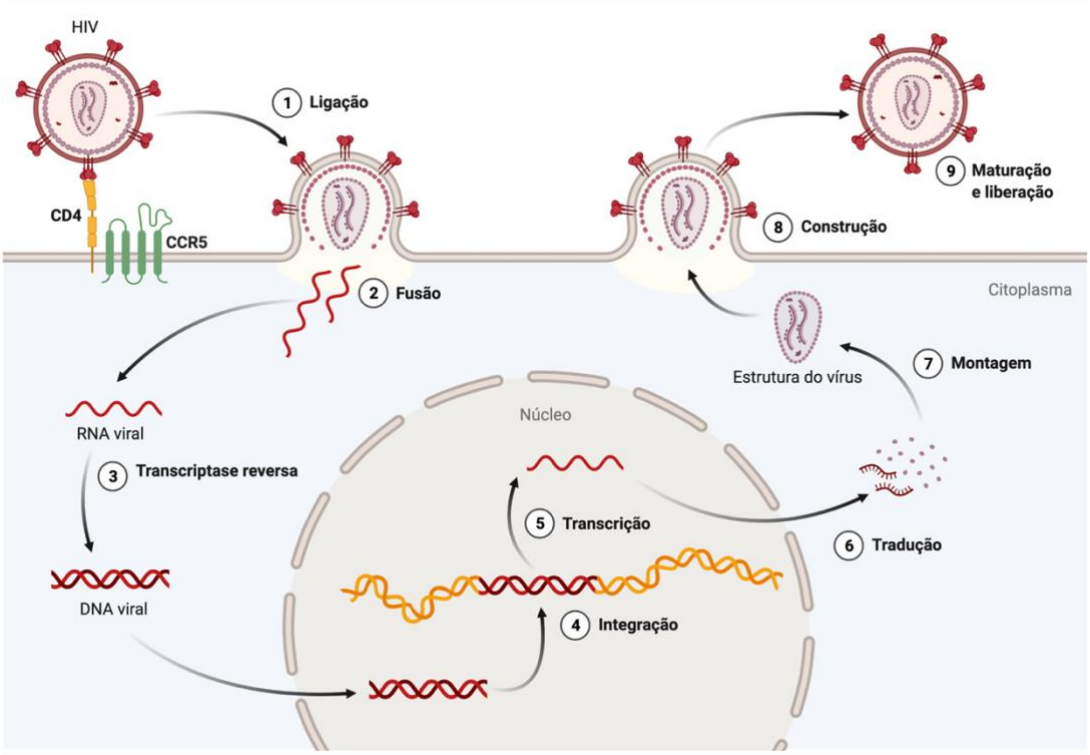

Figura 2. Ciclo de replicação do vírus da imunodeficiência humana. Legenda: grupo de diferenciação 4 (CD4), C-C receptor de quimiocina tipo 5 (CCR5), ácido ribonucleico (RNA), acido desoxiribonucleico (DNA). Adaptado e traduzido de ENGELMAN e CHEREPANOV (2012).

1.1.3 Terapia antirretroviral

As TARVs são categorizadas em diferentes classes, de acordo com a etapa em que inibem a replicação viral. A **Figura 3** ilustra os sítios de atuação das TARVs para inibição da replicação do HIV.

Seguindo as etapas de replicação viral, os inibidores de CCR5 atuam bloqueando a interação entre a GP120 e o CCR5. Isso ocorre após a ligação destes medicamentos ao CCR5, impedindo que o vírus se ligue à GP120 (BRIZ; POVEDA; SORIANO, 2006). Os inibidores de fusão (IF) atuam como bloqueadores das proteínas envelope, impedindo a interação entre a GP41 e as proteínas da célula alvo (LALEZARI; HENRY; O'HEARN; MONTANER *et al.*, 2003).

Os inibidores nucleosí(tí)dicos da transcriptase reversa (INTR) atuam por meio de fosforilações mediadas por quinases, sendo convertidos em formas que apresentam dois ou três fosfatos. Estas formas se ligam em suas respectivas bases nucleosídicas ou nucleotídicas análogas, fenômeno que causa a interrupção da síntese do DNA viral devido à ausência do grupo 3-hidroxil no INTR (HOLEC; MANDAL; PRATHIPATI; DESTACHE, 2017). Logo, trata-se de um mecanismo de inibição por competição, diferentemente dos inibidores não

nucleosídicos da transcriptase reversa (INNTR), que inibem a transcriptase reversa de maneira não-competitiva. Por exemplo, os INNTR não são dependentes do metabolismo intracelular, ou seja, não necessitam de fosforilações mediadas por quinases. Os INNTR podem inibir a replicação viral em diferentes etapas, geralmente categorizadas em pré e pós-integração. A etapa pré-integração, ainda no citosol, consiste basicamente na ligação que o INNTR faz ao sítio da transcriptase reversa que, por sua vez, atua na primeira etapa de transferência da fita do RNA viral. Este processo impede a ação sinérgica entre a DNA polimerase da célula e a RNase H viral. O processo de inibição pós-integração está relacionado a alteração das proteínas regulatórias do HIV, a $Pr55^{gag}$ (Gag) e a $Pr160^{gag\text{-}pol}$ (Gag-Pol). Estas proteínas são responsáveis pela formação da matriz, do capsídeo e do nucleocapsídeo que, quando inibidas, impossibilitam a formação completa do HIV (SLUIS-CREMER; TACHEDJIAN, 2008).

A integrase é uma enzima do HIV cuja função é clivar as ligações fosfodiester próximas às extremidades do DNA viral, permitindo que este se ligue ao DNA da célula invadida. Este processo é mediado pelos cátions divalentes de magnésio, possibilitando uma ligação covalente ao DNA. Os inibidores da integrase (INI) impedem que o DNA viral se acople ao DNA da célula do hospedeiro, processo que é mediado, principalmente, pelo impedimento da formação das ligações covalentes (POWDERLY, 2010).

Quando o DNA viral se liga ao DNA da célula do hospedeiro ocorre o processo transcrição, formando novas fitas de RNA viral que, ao serem encaminhadas ao citosol, são traduzidas em poliproteínas do vírus. Estas poliproteínas sofrem ação da enzima protease, cuja função é permitir, sobretudo, que as diversas proteínas virais fundamentais do HIV sejam formadas (p. ex., gag e pol). Os inibidores de protease (IP) se ligam aos sítios de ação da protease impedindo que as poliproteínas sejam clivadas e formem as pequenas e funcionais proteínas virais (p. ex., vif, vpr, vpu, nef). Esse processo inibe a montagem do vírus e, por consequência, sua maturação (WANG; CHAI; YAO; CHEN, 2007).

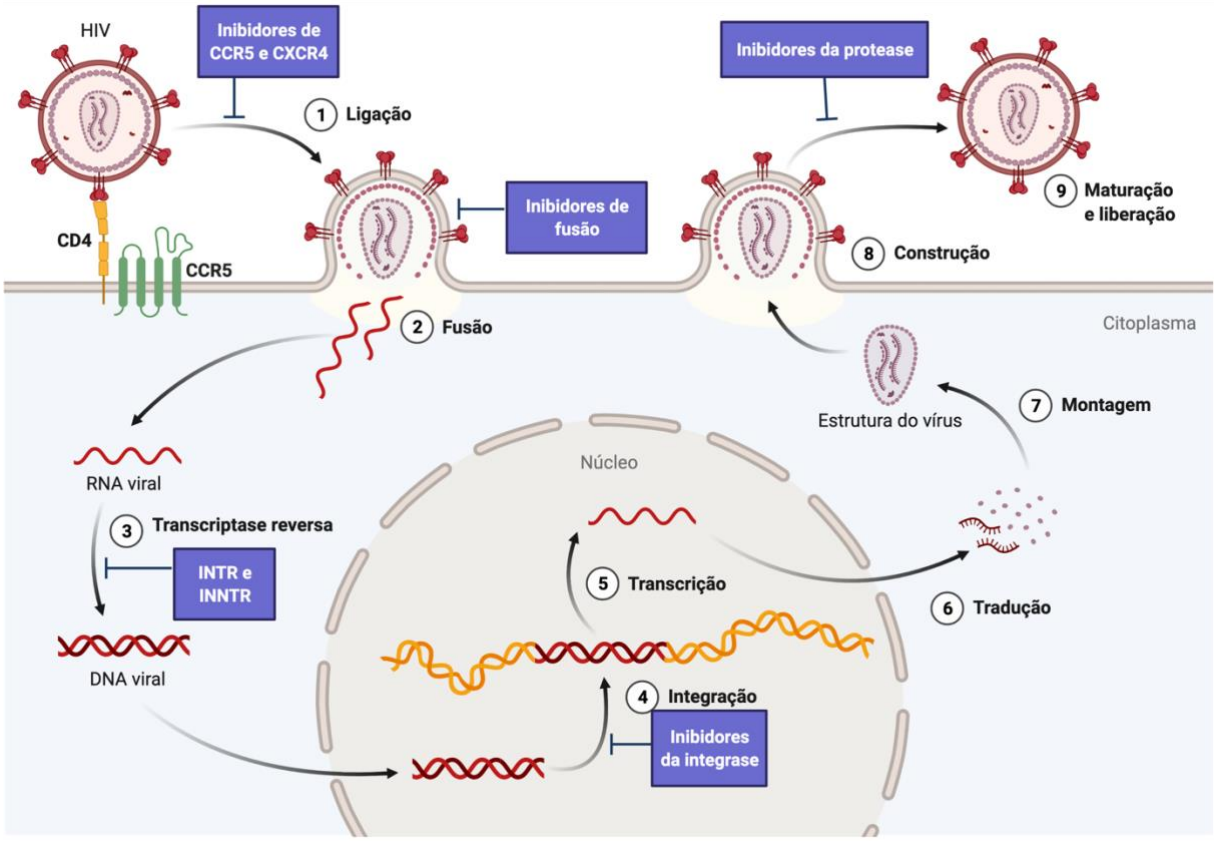

Figura 3. Etapas de atuação dos antirretrovirais no processo de replicação do vírus da imunodeficiência humana. Legenda: cluster de diferenciação 4 (CD4), C-C receptor de quimiocina tipo 5 (CCR5), ácido ribonucleico (RNA), acido desoxiribonucleico (DNA), inibidores nucleosí(tí)dicos da transcriptase reversa (INTR), inibidores não nucleosídicos da transcriptase reversa (INNTR). Adaptado e traduzido de ENGELMAN e CHEREPANOV (2012).

O primeiro medicamento aprovado para controle do HIV foi a Zidovudina (AZT), em 1987, um análogo de timidina que pertence a classe dos INTR. Outras classes de medicamentos foram criadas, por exemplo, em 1995, foi aprovado o Saquinavir, um IP. Já em 1996, foi aprovada a Nevirapina, que pertence a classe dos INNTR. Em 2003, foi aprovado o primeiro IF, o Enfuvirtida e, mais recentemente, em 2007, o Raltegravir, o primeiro INI (VELLA; SCHWARTLANDER; SOW; EHOLIE *et al.*, 2012). Ao longo do tempo, em decorrência da resistência aos medicamentos e dos efeitos adversos, novos medicamentos das diferentes classes foram criados com intuito de possibilitar um tratamento mais efetivo com menos efeitos colaterais. O **Quadro 1** apresenta os principais medicamentos antirretrovirais, a classe e ano de aprovação.

Quadro 1. Classe, medicamentos e ano de aprovação das terapias antirretrovirais.

INTR	INNTR	IP	IF/IA	INI	Ano de aprovação
Zidovudina					1987
Didanosina					1991
Zalcitabina					1992
Estavudina					1994
Lamivudina		Saquinavir			1995
	Nevirapina	Ritonavir, Indinavir			1996
	Delavirdina	Nelfinavir			1997
Abacavir	Efavirenz				1998
		Amprenavir			1999
		Lopinavir/ritonavir			2000
Tenofovir					2001
	Emtricitabina				2002
		Atazanavir	Enfuvirtida		2003
		Fosamprenavir			2004
		Tipranavir			2005
		Darunavir			2006
			Maraviroc	Raltegravir	2007
	Etravirina				2008
					2009
					2010
	Relpivirina				2011
				Dolutegravir	2013

Legenda: Inibidores nucleosí(tí)dicos da transcriptase reversa (INTR), Inibidores não nucleosídicos da transcriptase reversa, Inibidores da protease (IP), Inibidores de entrada (IA), inibidores de fusão (IF), Inibidores da integrase. Traduzido e adaptado de VELLA; SCHWARTLANDER; SOW; EHOLIE *et al.* (2012).

Inicialmente, a monoterapia era proposta com o uso de AZT; entretanto, os resultados foram pouco satisfatórios na restauração dos linfócitos T $CD4^+$ e na sobrevida das PVHIV. À medida que os outros medicamentos foram aprovados, a combinação de TARVs foi indicada para tentar promover efeitos mais positivos na inibição da replicação viral. Por exemplo, ainda no início da epidemia, a combinação da AZT com a didanosina aumentou a contagem de linfócitos T $CD4^+$ e a sobrevida em relação ao uso isolado da AZT (VELLA; SCHWARTLANDER; SOW; EHOLIE *et al.*, 2012). Contudo, apesar dos efeitos mais satisfatórios com a combinação dos medicamentos, uma série de efeitos adversos foram observados. Algumas pessoas que utilizaram a AZT apresentaram neutropenia, anemia, náusea e vômito (VELLA; SCHWARTLANDER; SOW; EHOLIE *et al.*, 2012). Além disso, a AZT, de maneira dose-dependente, levava a desordens no DNA pela inibição da polimerase-α celular e γ-polimerase mitocondrial. Este efeito da AZT sobre a mitocôndria impacta diretamente o

metabolismo energético, interferindo na cadeia de transporte de elétrons (CTE) e na capacidade de produzir adenosina trifosfato (ATP) (BARILE; VALENTI; QUAGLIARIELLO; PASSARELLA, 1998).

Além dos efeitos deletérios da monoterapia com AZT, muitos indivíduos apresentavam resistência ao tratamento. Neste sentido, o advento da Lamivudina (3TC), um análogo de citidina, permitiu resultados mais satisfatórios, principalmente, quando combinada à AZT ou à Estavudina. Embora algumas pessoas tenham mantido o uso da AZT, os análogos de timidina foram menos prescritos ao longo do tempo, haja vista os seus efeitos negativos (VELLA; SCHWARTLANDER; SOW; EHOLIE *et al.*, 2012).

A utilização da nevirapina, um INNTR, e dos IP, saquinavir ou ritonavir, foi prontamente proposta após as suas aprovações. No mesmo período, o indinavir, um IP, também foi utilizado, fazendo parte da terapia antirretroviral altamente ativa (do inglês, *Highly Active Antiretroviral Therapy* - HAART) juntamente à AZT e à 3TC (VELLA; SCHWARTLANDER; SOW; EHOLIE *et al.*, 2012). No fim dos anos 90, mais especificamente em 1998, após a introdução da HAART, alguns estudos foram publicados mostrando os resultados positivos do tratamento com antirretrovirais na redução da morbimortalidade das PVHIV. Em 2004, o tenofovir (TDF), o primeiro inibidor nucleotídico da transcriptase reversa foi aprovado e, no mesmo ano, também foi aprovada a proposta de um único medicamento, combinando emtricitabina e TDF. Reforça-se que, até os dias atuais, a combinação de princípios ativos em apenas um medicamento facilita o uso pelos pacientes e reflete diretamente na melhor adesão ao tratamento (DORMAN; SUTTON; YEE, 2019).

Em seguida, em 2007, a aprovação do raltegravir possibilitou o uso de uma nova classe de TARVs, os INIs. Atualmente, no entanto, sugere-se a troca do raltegravir por dolutegravir (DTG), um INI de nova geração que apresenta menor capacidade de resistência e menos efeitos adversos (CAHN; POZNIAK; MINGRONE; SHULDYAKOV *et al.*, 2013; RAFFI; RACHLIS; STELLBRINK; HARDY *et al.*, 2013).

No Brasil, em 2018, o Protocolo Clínico e Diretrizes Terapêuticas para manejo da infeção pelo HIV em adultos foi publicado. Este, por sua vez, com base nas evidências científicas mais atuais sobre as TARVs, sugere como esquema terapêutico preferencial para início de tratamento a 3TC e o TDF associados ao DTG. Comparativamente aos medicamentos de antiga geração, a combinação da 3TC e do TDF promoveu menor toxicidade, melhor controle da carga viral e melhor restauração dos linfócitos T $CD4^+$ (MINISTÉRIO DA SAÚDE, 2018).

As TARVs modificaram de maneira decisiva o cenário de mortalidade das PVHIV. Alguns estudos de coorte têm demonstrado que PVHIV apresentam expectativas de vida próximas às pessoas não infectadas (BENZAKEN; PEREIRA; COSTA; TANURI *et al.*, 2019) (ANTIRETROVIRAL THERAPY COHORT, 2017). Todavia, fatores como nível socioeconômico, etnia, contagem de linfócitos T $CD4^+$ no início do tratamento, o estilo de vida (p. ex., alcoolismo e tabagismo), e pertencer ao grupo população chave, interferem efetivamente na expectativa de vida dessa população. Por exemplo, no estudo de Samji *et al*. (2013) foram avaliadas 22.937 PVHIV com idade ≥ 20 anos de idade. Os autores observaram estimativas de expectativa de vida similar às pessoas não infectadas no mesmo período (ARIAS; HERON; XU, 2016). Em contraste, as estimativas de expectativa de vida foram inferiores para pessoas infectadas por uso de drogas injetáveis, em relação aos homens que fazem sexo com homens. De maneira semelhante, a expectativa de vida entre as PVHIV não brancas foi menor em comparação as brancas e, por fim, a expectativa de vida para pessoas que iniciaram o tratamento com a contagem de linfócitos T $CD4^+ < 350$ células/mm^3 foi de aproximadamente 16 anos menor comparativamente àqueles que iniciaram com valores de $CD4^+ \geq$ a 350 células/mm^3 (SAMJI; CESCON; HOGG; MODUR *et al.*, 2013). Finalmente, no que se refere às TARVs, a mudança da classe promoveu diferentes taxas de expectativa de vida (ANTIRETROVIRAL THERAPY COHORT, 2017). A partir destes resultados, destaca-se que o aumento da expectativa de vida das PVHIV utilizando antirretrovirais depende de diferentes fatores.

A respeito dos antirretrovirais no Brasil, em 1996, foi o primeiro país em desenvolvimento a oferecer as TARVs para todas as PVHIV. Ademais, com base nos dados do observatório global de saúde da OMS, no Brasil, a cobertura das TARVs entre as PVHIV passou de 34% em 2002 para 70% em 2020. Em 2017, o número de PVHIV tratadas com a carga viral suprimida era de 92% (BENZAKEN; PEREIRA; COSTA; TANURI *et al.*, 2019). Portanto, o Brasil se destaca como um dos principais países no combate ao HIV/AIDS.

Apesar do avanço no tratamento do HIV/AIDS e do aumento da sobrevida das PVHIV no Brasil e no mundo, deve-se ressaltar que diversas discussões são feitas sobre o desenvolvimento de doenças não-AIDS nessa população. Já no início dos anos 2000, surgiram as primeiras evidências sobre o aparecimento de desordens metabólicas e do entendimento de que as PVHIV apresentam um importante componente inflamatório que participa de maneira significativa no desenvolvimento de doenças crônicas não transmissíveis (BAKER; PENG; RAPKIN; ABRAMS *et al.*, 2008; BAKER; PENG; RAPKIN; KRASON *et al.*, 2008; BARBER; HUGHES; DINSMORE; PHILLIPS, 2009; BEDIMO, 2008; CONTI; MASOCCO; PEZZOTTI; TOCCACELI *et al.*, 2002; PACHECO; TUBOI; FAULHABER; HARRISON *et*

al., 2008). Ainda, neste período, foi publicado um dos primeiros estudos sobre o envelhecimento antecipado das PVHIV (DEEKS; PHILLIPS, 2009).

Isso posto, há um constante questionamento "*É possível que haja uma "sobrecarga" de alterações imunológicas e metabólicas que implicam em maiores desordens em pessoas vivendo com HIV?"*.

Este questionamento possibilita conjecturar sobre os potenciais efeitos deletérios do HIV e das TARVs sobre os mais diferentes desfechos em saúde.

1.1.4 HIV, TARVs, imunoativação persistente e inflamação sistêmica de baixo grau

Como citado anteriormente, as TARVs possibilitaram mudanças significativas na expectativa de vida das PVHIV. Os esquemas adequados de antirretrovirais são capazes de reduzir a viremia para níveis abaixo dos limites de detecção (< 40 – 50 cópias/mL); e nessas condições, as concentrações de moléculas pró-inflamatórias (p. ex., IL-6, TNF-α, IL-1) e a imunoativação diminuem, sendo este efeito variado entre as classes de antirretrovirais (MARITATI; ALESSANDRO; ZANOTTA; COMAR *et al.*, 2020).

Contudo, apesar deste importante efeito, as PVHIV não alcançam níveis similares de mediadores pró-inflamatórios comparativamente às pessoas sem o vírus (JONG; LOUW; VAN GORP; MEIJERS *et al.*, 2010; LEDERMAN; CALABRESE; FUNDERBURG; CLAGETT *et al.*, 2011; NEUHAUS; JACOBS; BAKER; CALMY *et al.*, 2010).

Em 2007, Peter Hunt publicou um importante estudo discutindo o papel da imunoativação na patogênese do HIV, tendo como base algumas observações prévias, que demonstraram que mesmo as células T não infectadas pelo HIV apresentavam maior expressão de proteínas relacionadas à imunoativação, promovendo apoptose e morte celular. Além disso, foi verificado que comparativamente aos linfócitos T $CD8^+$, os linfócitos T $CD4^+$ foram considerados mais susceptíveis à imunoativação (HUNT, 2007). Alguns estudos publicados no início dos anos 2000 apontaram que em algumas PVHIV, mesmo com a carga viral controlada devido aos antirretrovirais, os linfócitos T $CD4^+$ do tecido linfoide associado ao intestino (GALT) não foram recuperados na mesma velocidade em relação aos presentes nos tecidos periféricos. Essa lentidão e dificuldade na recuperação dos linfócitos T $CD4^+$ intestinais se dava, especialmente, pelo atraso no início do tratamento (GUADALUPE; REAY; SANKARAN; PRINDIVILLE *et al.*, 2003). Os achados de Mehandru *et al.* (2004) após a análise de células imunológicas periféricas do sangue e da mucosa intestinal de PVHIV e pessoas não infectadas, demonstraram que o percentual de linfócitos T $CD4^+$ na mucosa

intestinal era de aproximadamente 15,7%, ao passo que das pessoas não infectadas era de 56,4%. A relação CD4:CD8 em PVHIV também era menor nas células da mucosa (0,2 células/mm^3) comparativamente às células sanguíneas (0,9 células/mm^3). Nas pessoas que não viviam com HIV, os valores da razão CD4:CD8 era de aproximadamente 1,3 células/mm^3 na mucosa intestinal e 1,7 células/mm^3 no sangue (MEHANDRU; POLES; TENNER-RACZ; HOROWITZ *et al.*, 2004).

Com base nestes resultados e de outros estudos, demonstrando que as alterações nas células imunológicas eram mantidas mesmo sob o uso das TARVs, aumentaram as discussões acerca da imunoativação persistente como um importante componente para desordens não-AIDS associadas ao HIV. Neste contexto, Deeks (2009) trouxe à tona a importância de se compreender os mecanismos que levam à imunoativação persistente e ao aumento do processo inflamatório em PVHIV sob uso das TARVs (DEEKS, 2009). Por exemplo, um estudo conduzido pelo seu grupo demonstrou que o atraso (~ 4 anos) para iniciar o tratamento com antirretrovirais favoreceu um cenário de lentificação e resistência para restauração dos linfócitos T $CD4^+$. Estes dados reforçaram achados anteriores ao demonstrar que ao iniciar a terapia com a contagem de linfócitos T $CD4^+ < 100$ células/mm^3 ou entre 100-200 células/mm^3 não foi possível alcançar, após 7,5 anos, contagens ≥ 500 células/mm^3, comparativamente àqueles que iniciaram os antirretrovirais até os primeiros 10 meses com valores de $CD4^+ \geq 300/mm^3$ (KELLEY; KITCHEN; HUNT; RODRIGUEZ *et al.*, 2009).

Outros estudos foram publicados acerca da imunoativação persistente e da importância de iniciar a TARV antecipadamente, com intuito de evitar a redução de linfócitos T $CD4^+$ e possibilitar uma melhor restauração imunológica. Uma ampla revisão publicada por Nasi *et al*. (2014) estabeleceu a imunoativação persistente como a principal via para o desenvolvimento das doenças não-AIDS associadas ao HIV (NASI; PINTI; DE BIASI; GIBELLINI *et al.*, 2014). No mesmo ano, McComsey *et al*. conduziram um estudo com dados secundários do estudo randomizado A5202 do *AIDS Clinical Trials Group* e mostraram que os níveis elevados de marcadores inflamatórios (p. ex., IL-6, sICAM-1, PCR) foram associados a eventos não relacionados à AIDS em 244 PVHIV, como diabetes mellitus, doença hepática e doenças cardiovasculares (MCCOMSEY; KITCH; SAX; TIERNEY *et al.*, 2014).

Outros fatores relacionados aos antirretrovirais estão associados à persistente imunoativação observada em PVHIV; portanto, além do maior tempo entre a infecção e o início do tratamento como citado acima, o número de medicamentos, a má adesão ao tratamento, a resistência ao esquema terapêutico e as diferentes classes de medicamentos, explicam, ao menos

em parte, a maior imunoativação observada em PVHIV em comparação a pessoas não infectadas.

No que tange o número de medicamentos, Serrano-Villar *et al*. (2022) avaliaram marcadores inflamatórios de 148 PVHIV. Destes, 90 estavam utilizando três medicamentos associados e 58 estavam utilizando dois medicamentos associados. Os autores verificaram que o uso de três antirretrovirais possibilitou um declínio gradual de mediadores inflamatórios, como IL-6, PCR, e D-dímero, sem diferenças no *Intestinal Fatty Acid Biding Protein* (IFABP), CD14 solúvel (sCD14), sCD163 após 4 anos em relação ao início do tratamento. O uso de apenas dois antirretrovirais promoveu níveis mais elevados de IL-6, PCR e D-dímero comparativamente ao grupo que usou três medicamentos (SERRANO-VILLAR; LOPEZ-HUERTAS; JIMENEZ; GALERA *et al.*, 2022).

Outro aspecto importante para verificar a trajetória dos mediadores inflamatórios ao longo do tempo em PVHIV é o tipo de TARV. Diversas combinações são propostas e, para além da classe, medicamentos específicos promovem efeitos heterogêneos, o que dificulta a interpretação dos achados. Em um estudo *open-label* do AIDS *Clinical Trials Group*, foram avaliados marcadores de ativação de monócitos (p. ex., HLA-DR, CD86, CCR2 e CX3CR1) após o uso de raltegravir associado ao TDF e emtricitabina. Os autores observaram que todos os marcadores foram reduzidos a níveis próximos aos de pessoas não infectadas (SAX; DEJESUS; MILLS; ZOLOPA *et al.*, 2012).

Outro estudo comparou o uso de elvitegravir/ cobiscistate/ TDF/ emtricitabina *vs*. efavirenz/ TDF/ emtricitabina em pessoas que nunca utilizaram TARVs. Após 48 semanas de intervenção, os autores avaliaram diferentes marcadores de imunoativação (p. ex., PCR, IL-6, receptor de TNF-α, CD14 e CD163 solúvel). Apesar de todos os marcadores diminuírem em ambos os grupos, naqueles que usaram o raltegravir, a magnitude de redução foi maior (HILEMAN; KINLEY; SCHAREN-GUIVEL; MELBOURNE *et al.*, 2015).

Em outro estudo do ACTG, os autores avaliaram três grupos que nunca utilizaram TARVs, submetendo-os as seguintes intervenções: (i) TDF/ emtricitabina/ raltegravir; (ii) TDF/ emtricitabina/ atazanavir/ ritonavir; (iii) TDF/ emtricitabina/ darunavir/ ritonavir. Após o experimento, todos os grupos exibiram carga viral indetectável (< 50 cópias/mL); ainda, os marcadores de ativação de monócitos solúveis e celulares (p. ex., D-dímero, PCR, IL-6) foram reduzidos de maneira heterogênea, enquanto apenas o sCD163 reduziu de maneira similar entre os grupos (LENNOX; LANDOVITZ; RIBAUDO; OFOTOKUN *et al.*, 2014).

Enquanto alguns estudos não observaram redução de sCD14 e sCD163 após o uso de INTR e IP (HATTAB; GUIHOT; GUIGUET; FOURATI *et al.*, 2014; RUDY;

KAPOGIANNIS; WORRELL; SQUIRES *et al.*, 2015), os INI parecem reduzir de maneira mais eficiente os mediadores inflamatórios por ficarem mais retidos nos enterócitos e, como já descrito, o intestino é um dos principais reservatórios de linfócitos T $CD4^+$ infectados pelo HIV. O uso de TDF também favoreceu resultados positivos em marcadores imunológicos (CASTILLO-MANCILLA; MEDITZ; WILSON; ZHENG *et al.*, 2015; FUNDERBURG; MCCOMSEY; KULKARNI; BANNERMAN *et al.*, 2016), apesar destes achados não serem conclusivos. Logo, entende-se que os esquemas terapêuticos atuais (p. ex., DTG; TDF e 3TC) promovem efeitos mais positivos sobre os mediadores inflamatórios (RASMUSSEN; MCMAHON; CHANG; AUDSLEY *et al.*, 2018) e reduzem moléculas relacionadas à imunoativação (p. ex., sCD14) (GONZALEZ-CORDON; ASSOUMOU; MOYLE; WATERS *et al.*, 2021).

A sustentação do ambiente inflamatório em PVHIV sob o uso de antirretrovirais perpassa por outros órgãos e tecidos, incluindo o TA. As mudanças que ocorrem no TA em PVHIV foram alvo de muitos estudos, haja vista que o TA desempenha um papel crítico no surgimento de doenças não-AIDS, similar ao que acontece em pessoas não infectadas e que vivem com obesidade (CHAIT; DEN HARTIGH, 2020). Assim, o aumento e a desregulação do TA também contribuem para instalação da ISBG.

O monitoramento dos efeitos das TARVs na década de 90 permitiu verificar alterações metabólicas desfavoráveis, como as mudanças no metabolismo dos lipídeos, em especial, a piora do perfil lipídico sanguíneo, marcada pelas elevadas concentrações de triacilglicerol (hipertrigliceridemia) e a lipodistrofia, que impactou diretamente na composição corporal das PVHIV. Alguns estudos publicados demonstraram que os IP favoreceram o desenvolvimento da lipoatrofia e/ou lipohipertrofia do TA, que foram caracterizadas pela redução e pelo aumento, respectivamente, do TA em alguns locais do corpo. O fenótipo da lipodistrofia consistia, em algumas pessoas, na combinação da lipoatrofia e da lipohipertrofia, promovendo mudanças relacionadas à redistribuição de triacilgliceróis pelo corpo. A principal alteração deste fenótipo se deu pela redução de gordura no rosto e nos membros periféricos, acompanhada do aumento de gordura na região abdominal (KOETHE; LAGATHU; LAKE; DOMINGO *et al.*, 2020). Ademais, no que diz respeito a lipohipertrofia, alguns indivíduos exibiam um aumento desproporcional de gordura em regiões como dorso-cervical, peitoral, suprainguinal e alguns lipomas distribuídos pelo corpo (GUARALDI; ORLANDO; SQUILLACE; ROVERATO *et al.*, 2007).

As ferramentas para determinação do fenótipo da lipodistrofia não eram bem estabelecidas, mas, com base nas avaliações clínicas da época, os dados de prevalência

variavam entre 13 a 70% na década de 1990 (DOMINGO; ESTRADA; LOPEZ-ALDEGUER; VILLAROYA *et al.*, 2012). Alguns estudos reportaram diferenças na prevalência de acordo com o sexo e a idade e, finalmente, observaram um fenômeno bifásico no TA de acordo com o tipo de TARV. Nos períodos da terapia isolada ou com apenas dois antirretrovirais, os análogos de timidina, como a AZT, promoveram aumento de gordura corporal no início do tratamento (24 – 32 semanas), seguida de reduções na ordem de 1,7 % a 19 % por ano dependendo da combinação dos medicamentos (KOETHE; LAGATHU; LAKE; DOMINGO *et al.*, 2020).

Destaca-se, ainda, que o aumento da massa corporal, sobretudo de gordura corporal devido aos efeitos das TARVs, não se limita aos antirretrovirais de antiga geração, como a AZT e o indinavir ou outros INTR e IP. Nos últimos anos, especialmente, na última década, novas medicações foram desenvolvidas e aprovadas, como o DTG, da classe dos INI. Neste contexto, Bourgi *et al*. (2020) avaliaram e monitoraram as PVHIV (87 % homens; 41 % brancos) que utilizaram diferentes esquemas terapêuticos, contendo INNTR, IP ou INI em um seguimento de 5 anos. Os autores observaram aumento da massa corporal de 5,9, 5,5 e 3,7 kg àqueles que utilizaram INI, IP e INNTR, respectivamente. Entre os que utilizaram INI, o efeito do DTG foi o mais significativo, uma vez que o aumento da massa corporal foi de 7,2 kg após 2 anos de tratamento (BOURGI; JENKINS; REBEIRO; PALELLA *et al.*, 2020).

Não estão bem estabelecidos os mecanismos que explicam as alterações no TA de PVHIV que utilizaram TARVs de antiga geração ou medicamentos mais novos. Alguns estudos sugerem que os fatores de transcrição pró-adipogênicos (p. ex., SREBP1) e os seus alvos, como o transportador de glicose do tipo 4 (GLUT-4) e lipase lipoproteica (LPL) estejam suprimidos comparativamente a pessoas não infectadas. Estas alterações levam à desregulação do metabolismo lipídico e glicídico, bem como a redução de adipocitocinas, como a adiponectina e a leptina. Estes dados, no entanto, sugerem que ambos, medicamentos de antiga e da nova geração, impactam negativamente no metabolismo lipídico (STIRES; LAMORI; CHOW; ZALEWSKI *et al.*, 2021).

O fenômeno da redistribuição de gordura citado acima favoreceu o aumento da gordura visceral, cujos componentes inflamatórios são bem estabelecidos (ALEXOPOULOS; KATRITSIS; RAGGI, 2014). Diferente de outras células, os adipócitos são capazes de aumentar em cenários de balanço energético positivo crônico e de desregulação metabólica. Geralmente, apresentam diâmetro de 30 – 40 μm e chegam a tamanhos acima de 100 μm; no entanto, à medida que o adipócito aumenta, a diferenciação de pré-adipócitos fica disfuncional, reduzindo a adipogênese. Em consequência, ocorre a hipertrofia dos adipócitos, caracterizada pelo aumento desregulado do conteúdo de triacilgliceróis. Este fenômeno promove a redução

da oxigenação no TA, o que desencadeia diferentes alterações, incluindo mudanças do sistema imunológico local. Células imunológicas que regulam a quimiotaxia ficam mais ativadas e aumentam o infiltrado de monócitos para o TA que, em seguida, são diferenciados em macrófagos, e aumentam a produção de citocinas inflamatórias (DALMAS; CLEMENT; GUERRE-MILLO, 2011). Simultaneamente, os macrófagos já residentes no TA são polarizados em macrófagos M1, exibindo maior perfil inflamatório (CYPESS, 2022; ZATTERALE; LONGO; NADERI; RACITI *et al.*, 2019).

O aumento da inflamação no TA leva à resistência à insulina, que ocorre devido a ativação de proteínas como IκB quinase e Janus quinase. Ambas participam da fosforilação do substrato do receptor de insulina 1 (IRS-1) nos resíduos dos aminoácidos serina e treonina, impedindo sua auto fosforilação no aminoácido tirosina e sinalização, que incorre na ativação do GLUT-4 e na captação de glicose. Ademais, este cenário no TA permite com que haja a ativação do complexo IKK quinase, que induz a degradação do IκBα, permitindo a translocação do fator nuclear kappa B (NF-κB) para o núcleo celular. O NF-κB aumenta a expressão de genes responsáveis pela formação de IL-6, TNF-α, interferon-γ, IL-1β e a proteína de quimiotaxia de monócitos 1 (MCP-1). Estas proteínas, além de aumentarem a resistência à insulina do TA, favorecem o desenvolvimento de um ambiente inflamatório. Além disso, as células mieloides do TA ativam o inflamassoma *NLR Family Pyrin Domain Containing 3* (NLRP3) em resposta aos padrões moleculares associados a patógenos (PAMPs) como, por exemplo, os fragmentos bacterianos e virais e padrões moleculares associados a danos (DAMPs) como as EROs. Essa ativação ocorre via receptores específicos, nomeados como receptores de reconhecimento de padrões, como o *toll-like receptor* (TLR), *NOD-like receptor* (NLR) e *RIG-like receptor* (RLR) (CYPESS, 2022; ZATTERALE; LONGO; NADERI; RACITI *et al.*, 2019). Estas modificações no TA que levam à inflamação estão aumentadas em PVHIV que usam TARVS que promovem lipohipertrofia. Ainda, independentemente da carga viral e da contagem de linfócitos T $CD4^+$, verifica-se a manutenção da inflamação (DE PAUW; TEJERINA; RAES; KEIJER *et al.*, 2009; VIDAL; DOMINGO; VILLARROYA; GIRALT *et al.*, 2012). Essas alterações também são resultantes das proteínas que acompanham o HIV no processo de replicação, como tat, vpr, vpu e nef que, na mitocôndria do TA, estimulam a produção de EROs e a ativação do NPLR3 inflamassoma, aumentando o ambiente inflamatório (KOETHE; LAGATHU; LAKE; DOMINGO *et al.*, 2020).

Em conjunto, estas mudanças promovem um ambiente pró-lipolítico do TA, aumentando a atividade das enzimas lipase triacilglicerol, lipase hormônio sensível e lipase

Monoacilglicerol, que medeiam a quebra do triacilglicerol em ácidos graxos livres (AGL). Além de diversas células imunológicas possuírem afinidade pelos AGL via TLR-4 e desencadear aumento da imunoativação, outros tecidos aumentam a captação de AGL. Por exemplo, o fígado e o ME captam mais AGL os quais, em seguida, ficam internalizados na forma de triacilglicerol, diacilglicerol, ceramidas, e esfingolipídios, que deflagram mais alterações imunológicas e metabólicas (KOETHE; LAGATHU; LAKE; DOMINGO *et al.*, 2020).

Finalmente, além dos efeitos do próprio HIV no TA, estimulando vias de inflamação, o HIV afeta diretamente a microbiota intestinal (MI) e as células epiteliais intestinais (CEI) (MUDD; BRENCHLEY, 2016). É importante reforçar que, de maneira geral, os antirretrovirais não atuam eficientemente no intestino como citado anteriormente.

Após a infecção pelo HIV, verifica-se rapidamente mudanças no perfil de células imunológicas do intestino, especialmente pela redução dos linfócitos T $CD4^+$ e desregulação dos linfócitos Th17, com consequente redução das interleucinas 17 e 22, que exercem um importante papel na manutenção da integridade da barreira intestinal (MUDD; BRENCHLEY, 2016). Embora os linfócitos Th17 não sejam os únicos responsáveis por produzir IL-17 no intestino, outras células (p.ex., DC e células linfoides inatas) que desempenham essa função, também estão alteradas nas PVHIV (MUDD; BRENCHLEY, 2016).

Ainda, verifica-se redução da riqueza e da diversidade bacteriana intestinal, com consequente aumento das bactérias patobiontes, redução das bactérias comensais e comprometimento da função de barreira (VUJKOVIC-CVIJIN; SOMSOUK, 2019). Comparadas às pessoas sem o HIV, as PVHIV apresentam aumento de *Prevotella* e redução de *Bacteroides*. Algumas espécies derivadas do gênero *Prevotella* aumentam a inflamação da mucosa intestinal mediada pela menor atividade dos linfócitos Th17, enquanto algumas espécies do gênero *Bacteroides* estão associadas a redução do ambiente inflamatório intestinal, especialmente, pelo aumento de células natural killer (NK) no GALT (GOOTENBERG; PAER; LUEVANO; KWON, 2017; KOAY; SIEMS; PERSAUD, 2018; LING; JIN; XIE; CHENG *et al.*, 2016). Além disso, a menor abundância de bactérias produtoras de butirato – um dos mais importantes ácidos graxos de cadeia curta (AGCCs) e indispensável à função de barreira – foi correlacionada a maiores concentrações plasmáticas do sCD14 (SERRANO-VILLAR; VAZQUEZ-CASTELLANOS; VALLEJO; LATORRE *et al.*, 2017).

As mudanças na composição bacteriana intestinal e o comprometimento da função barreira levam ao aumento da permeabilidade intestinal, permitindo que moléculas como o lipopolissacarídeo (LPS), um fragmento da parede celular de bactérias gram-negativas, alcance

o GALT, a corrente sanguínea e, em última instância, provoque endotoxemia metabólica, reconhecida por elevadas concentrações de LPS (MAZGAEEN; GURUNG, 2020).

Uma vez na circulação, o LPS se liga à proteína de ligação de lipopolissacarídeo (LPB), uma proteína plasmática tipicamente expressa, que facilita a interação entre o LPS e os TLRs, especialmente, o TLR-4. Os TLRs são expressos por células imunes, incluindo macrófagos, DC e células não imunes, como as células endoteliais, adipócitos e miócitos (MAZGAEEN; GURUNG, 2020). Os TLRs são eficientes no reconhecimento de PAMPs derivados de microrganismos, como LPS, e deflagram uma resposta inflamatória por meio da ativação do NF-κB, culminando no aumento da transcrição e tradução de citocinas pró-inflamatórias, como IL-6 e TNF-α (MAZGAEEN; GURUNG, 2020). A ativação excessiva e prolongada dos TLRs, particularmente do TLR-4, pode impulsionar respostas imunológicas desreguladas locais e sistêmicas, colaborando para manutenção da ISBG. Em PVHIV, o LPS aumenta a imunoativação dos linfócitos T $CD8^+$ (BRENCHLEY; PRICE; SCHACKER; ASHER *et al.*, 2006); logo, a menor razão CD4:CD8 pode ilustrar um quadro de manutenção da imunoativação e da ISBG (CABY; GUIHOT; LAMBERT-NICLOT; GUIGUET *et al.*, 2016).

Finalmente, é possível considerar uma importante relação entre o TA e a MI. Produtos provenientes da MI podem alcançar o TA, ativando vias inflamatórias. Portanto, o eixo microbiota-intestino-tecido adiposo pode ser um importante componente da imunoativação persistente e ISBG em PVHIV (LUNDGREN; THAISS, 2020). Recentemente, Gelpi *et al.* (2022) verificaram que as PVHIV apresentam menos triptofano no intestino e maior razão quinurenina:triptofano. Além disso, verificaram que a maior razão quinurenina:triptofano foi associada a uma maior razão gordura visceral-gordura subcutânea (GELPI; VESTAD; RAJU; HANSEN *et al.*, 2022). A quinurenina é uma substância proveniente do metabolismo do triptofano que geralmente está em elevadas concentrações quando uma enzima chamada indoleamina (IDO) está supra regulada. A imunoativação persistente e a ISBG estão associadas a maior atividade da IDO e, por consequência, da conversão do triptofano em quinurenina. Outro estudo de Gelpi *et al.* revelou que a maior quantidade de gordura central foi associada a maior atividade da via da quinurenina em PVHIV, sugerindo que este mecanismo também contribui para ISBG em PVHIV (GELPI; UELAND; TROSEID; MOCROFT *et al.*, 2020).

As alterações supracitadas explicam, mesmo que parcialmente, o quadro de ISBG nas PVHIV (DESAI; LANDAY, 2010; FURMAN; CAMPISI; VERDIN; CARRERA-BASTOS *et al.*, 2019; HOENIGL; KESSLER; GIANELLA, 2019; WING, 2016) e, além disso, é indispensável destacar que muitas e relevantes similaridades são observadas entre as PVHIV e os idosos, principalmente no que diz respeito à instalação de um ambiente inflamatório. Estas

similaridades reforçam a hipótese do envelhecimento antecipado em PVHIV, tendo como critério a observação de mudanças fisiológicas que ocorrem em idosos (idades > 60 anos) acontecerem nas PVHIV mais jovens (40 – 50 anos). Portanto, algumas mudanças esperadas no envelhecimento celular fisiológico nas PVHIV seriam compatíveis ao envelhecimento cronológico observado nos idosos.

1.1.5 Similaridades entre o envelhecimento e as PVHIV

Alguns estudos longitudinais mostraram que o número de PVHIV com idade ≥ 50 anos é crescente e supera – em alguns países – o número de pessoas jovens e adultas vivendo com HIV (NEGIN; GREGSON; EATON; SCHUR *et al.*, 2016). Neste novo cenário epidemiológico, as discussões acerca do envelhecer com HIV vêm ganhando mais atenção pela comunidade científica.

Múltiplos estudos publicados nos últimos anos apontaram para as similaridades entre as PVHIV e os idosos, principalmente, no que se refere às alterações do sistema imunológico que favorecem o desenvolvimento do ambiente pró-inflamatório conhecido como ISBG (CASTILHO; SHEPHERD; KOETHE; TURNER *et al.*, 2016; CHAUVIN; SAUCE, 2022; DEEKS, 2011; LAGATHU; COSSARIZZA; BEREZIAT; NASI *et al.*, 2017; LOPERA; LUJAN; ZUREK; ZAPATA *et al.*, 2021; NDUMBI; GILBERT; TSOUKAS, 2015; NOVAK; ARMON; BATTALORA; BUCHACZ *et al.*, 2022; QUIROS-ROLDAN; PROPERZI; PAGHERA; RAFFETTI *et al.*, 2020; SERRANO-VILLAR; SAINZ; LEE; HUNT *et al.*, 2014).

O envelhecimento leva a diferentes alterações fisiológicas e metabólicas que, em diversas situações, alteram a atividade de células do sistema imunológico, de órgãos e de tecidos, que contribuem para a instalação da ISBG. Para idosos, a ISBG, também descrita como *Inflammaging* (FRANCESCHI; BONAFE; VALENSIN; OLIVIERI *et al.*, 2000; FRANCESCHI; SALVIOLI; GARAGNANI; DE EGUILEOR *et al.*, 2017) é atribuída, principalmente, a três importantes alterações. A imunossenescência, a senescência celular e a inflamação metabólica.

1.1.5.1 Imunossenescência

A imunossenescência é caracterizada por um estado funcional de declínio do sistema imunológico (PADILHA DE LIMA; MACEDO ROGERO; ARAUJO VIEL; GARAY-

MALPARTIDA *et al.*, 2022). As respostas imunológicas humorais e celulares contra patógenos ficam menos eficientes. Este declínio pode ser atribuído as alterações em receptores, mudanças nos subtipos de células imunológicas e a sinalização celular mediada por células imunológicas ineficientes ou desreguladas (CROOKE; OVSYANNIKOVA; POLAND; KENNEDY, 2019). Algumas alterações no sistema imunológico marcam a imunossenescência, tais como a involução do timo e o envelhecimento da medula óssea (PADILHA DE LIMA; MACEDO ROGERO; ARAUJO VIEL; GARAY-MALPARTIDA *et al.*, 2022).

O envelhecimento modifica ambos, o sistema imune inato e adaptativo. No que se refere ao sistema imunológico inato, os neutrófilos, monócitos, macrófagos, as células NK e as DC modificam suas características e contribuem para a imunossenescência. Sem a presença da imunosenescência, os neutrófilos, principal classe de fagócitos, migram até o local de inflamação e liberam citocinas inflamatórias (p. ex., IL-1, IL-8 e TNF-α). Ainda, os neutrófilos quando migram e infiltram no tecido inflamado, fagocitam e liberam peptídeos antimicrobianos para resolução da inflamação. No envelhecimento, os neutrófilos sofrem alterações moleculares, como a desregulação da proteína fosfoinositol-3 quinase (PI3K), responsável pela migração dos neutrófilos. Ademais, a respeito das alterações celulares nos neutrófilos, destaca-se a menor expressão dos receptores de superfície, como o CD16. Ambas as alterações impactam negativamente nos processos de migração, fagocitose e liberação de citocinas. Ainda, geralmente, após a resolução da inflamação, os neutrófilos sofrem apoptose. Contudo, no envelhecimento, os neutrófilos são antecipadamente direcionados à apoptose, comprometendo a resposta contra infecções (CROOKE; OVSYANNIKOVA; POLAND; KENNEDY, 2019).

Os monócitos e os macrófagos também exercem importante função fagocítica. Monócitos se diferenciam em macrófagos quando migram para os tecidos, os quais, são amplamente plásticos e responsivos a diferentes estímulos. Nos idosos, similar aos neutrófilos, os macrófagos exibem menor capacidade de fagocitose. Ademais, a desregulada produção de citocinas, a maior expressão de TLR e a menor capacidade autofágica explicam as respostas inflamatórias desreguladas e a hiper-reatividade dos macrófagos (DE MAEYER; CHAMBERS, 2021).

As células NK são citotóxicas e compreendem ~ 15% da população de linfócitos circulatórios. Estas são subdividas de acordo com o CD56, em $CD56^{dim}$ e $CD56^{bright}$. O $CD56^{dim}$ é mais citotóxico, enquanto o $CD56^{bright}$ é mais regulatório. Ao longo do envelhecimento, principalmente o $CD56^{dim}$, se expande e expressa mais CD57, que exibe maior capacidade citotóxica, mas são menos responsivos às citocinas. Simultaneamente, os $CD56^{bright}$ diminuem

e ficam menos eficientes para produzir e liberar citocinas e quimiocinas regulatórias (LE GARFF-TAVERNIER; BEZIAT; DECOCQ; SIGURET *et al.*, 2010; LOPEZ-VERGES; MILUSH; PANDEY; YORK *et al.*, 2010).

As DC são as principais células apresentadoras de antígenos (APCs) nas mucosas e atuam como uma ponte entre o sistema imune inato e o adaptativo. Dentre as suas funções, destaca-se a habilidade de apresentar antígenos aos linfócitos T. Similar às células NK, as DC também se subdividem, sendo mieloides (mDC), plasmocitoides (pDC) e foliculares (fDC). O envelhecimento das pDC diminui a capacidade de produzir interferons do tipo I e III, o que leva a menor fosforilação do IRF-7, um fator de transcrição que regula a expressão do TLR7 e TLR9. A menor fosforilação do IRF-7 aumenta a expressão do TLR7 e 9, ampliando o reconhecimento de diversas moléculas inflamatórias. As mDC de idosos fazem menos fagocitose e são menos quimiotáxicas em resposta à inflamação. Ainda, a atividade da proteína PI3K nas mDC está diminuída, o que aumenta o NF-κB e leva à maior produção de citocinas inflamatórias, mesmo na ausência de estímulos (AGRAWAL; GUPTA, 2011). As PVHIV exibem o mesmo perfil secretório, com as células NK ativadas constantemente, especialmente, no intestino, conforme recentemente descrito por Mikulak *et al*. (2020). A **Figura 4** ilustra as alterações na MI que explicam mudanças fenotípicas e a constante ativação das células NK intestinais que, por consequência, contribuem para manutenção da ISBG mesmo com os linfócitos T $CD4^+$ mantidos em PVHIV utilizando antirretrovirais.

O sistema imunológico adaptativo, sobretudo pelos linfócitos T e B, também é afetado com o envelhecimento. Dando destaque aos linfócitos T, em especial, o T $CD4^+$, responsável pela resposta humoral regulatória, e o T $CD8^+$, efetor e citotóxico, sugere-se que o número de linfócitos T nos idosos fique estável; entretanto, mudanças no seu subtipo marcam o processo de imunossenescência. A involução do timo citada anteriormente leva à menor produção de linfócitos T naïve e ao aumento dos linfócitos T de memória. Além disso, o CD28 reduz nos linfócitos T, levando à menor resposta imunológica. O TNF-α reduz a expressão do CD28 o que explica, ao menos em parte, o motivo pelo qual em situações de ISBG/*inflammaging* pode inviabilizar a resposta imune adequada. A maior relação linfócitos T de memória e menor linfócitos T naïve reduz a capacidade de lidar contra novos antígenos (SAULE; TRAUET; DUTRIEZ; LEKEUX *et al.*, 2006).

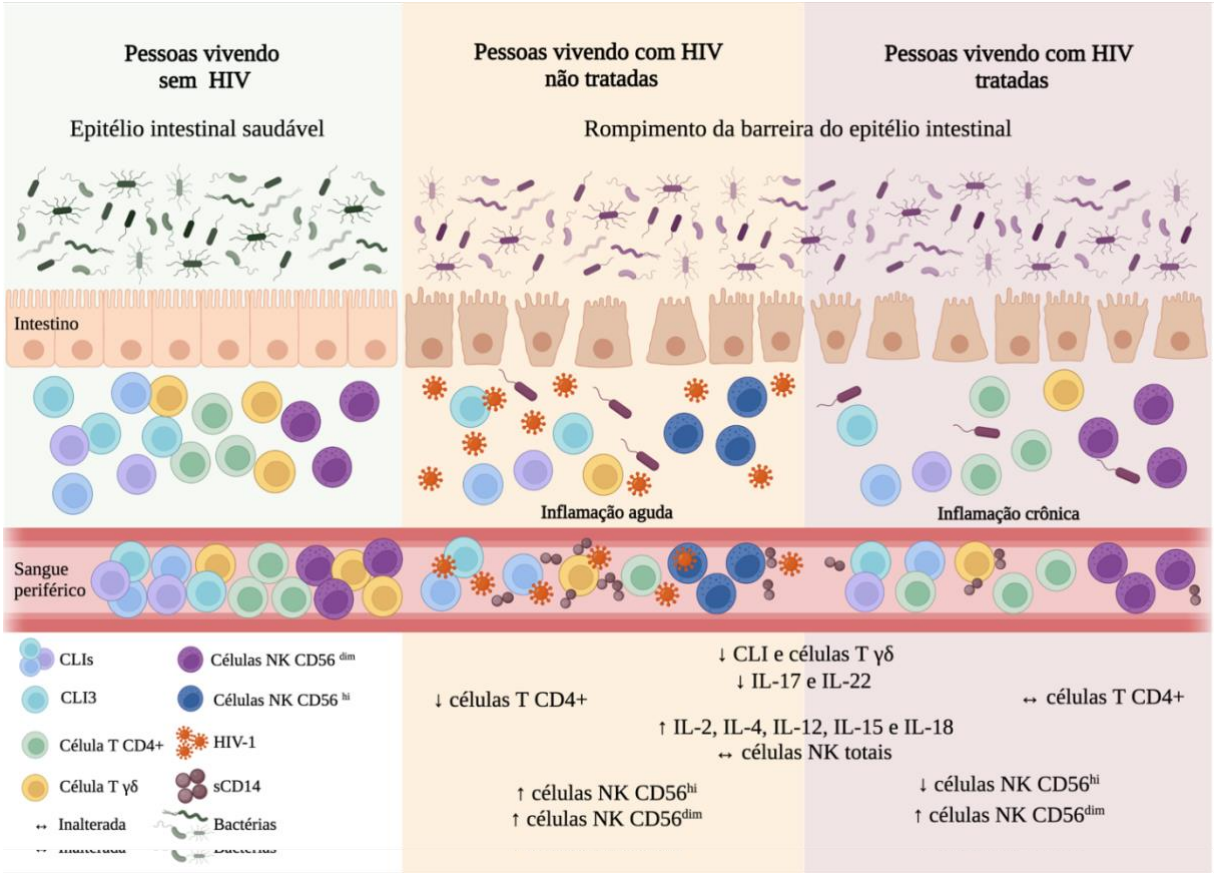

Figura 4. Alterações intestinais como mediadora da imunoativação persistente em PVHIV. Legenda: Células linfoides intestinais (CLIs), Natural Killer (NK), Interleucina (IL), CD14 solúvel (sCD14). Adaptado e traduzido MIKULAK; DI VITO e MAVILIO (2020).

Deeks (2011) trouxe a possibilidade de as PVHIV experimentarem um quadro de imunossenescência. Inclusive, sugere-se que a imunossenescência associada ao HIV contribui para a persistente imunoativação e ao antecipado surgimento de doenças não-AIDS. O **Quadro 2** ilustra as similaridades entre PVHIV e envelhecimento proposta por Deeks, porém, adicionada de similaridades com base nos achados após 2011.

Quadro 2. Similaridades entre PVHIV e idosos no que tange a imunossenescência.

Marcadores	Idade > 70 anos	HIV não tratado	PVHIV tratadas (5 – 10 anos)
Menor razão CD4:CD8	Sim	Sim	Sim
Menos linfócitos T naïve e mais linfócitos T memória	Sim	Sim	Sim
Menos CD28 em linfócitos T	Sim	Sim	Sim
Expansão de CD57 em linfócitos T	Sim	Sim	Sim
Redução do repertório de linfócitos T	Sim	Sim	Sim
Mais IL-6	Sim	Sim	Sim
Maior ativação de linfócitos T	Sim	Sim	Sim
Involução do timo	Sim	Sim	Sim

Legenda: Interleucina (IL), cluster de diferenciação (CD). Adaptado e traduzido de DEEKS (2011) e CHAUVIN e SAUCE (2022).

1.1.5.2 Senescência celular

A senescência celular é considerada um processo dinâmico, complexo e multifatorial, podendo ser caracterizada por alterações que favorecem mudanças irreversíveis em células que ficam em um estado "estacionário", resistentes à apoptose e com elevada capacidade de estimular vias metabólicas, incluindo autocrinas e parácrinas (PADILHA DE LIMA; MACEDO ROGERO; ARAUJO VIEL; GARAY-MALPARTIDA *et al.*, 2022). Diferente das células quiescentes, as células senescentes não proliferam em resposta a sinais adequados e específicos, que são geralmente mediados por fatores de crescimento ou sinais mitogênicos (KUMARI; JAT, 2021). Estas células senescentes, que podem estar danificadas, são capazes de secretar proteínas, metabólitos e resíduos como os DAMPs. Os DAMPs, por sua vez, podem ser componentes da matriz extracelular e intracelular; no entanto, os DAMPs derivados de compartimentos intracelulares, como citosol, núcleo e mitocôndria, são os mais frequentes, tais como o ATP, as histonas, o DNA, o DNA mitocondrial, entre outros. Estes DAMPs são reconhecidos por diferentes tipos de receptores pertencentes ao sistema imunológico inato

como os TLRs, NLRs e RLRs. Por exemplo, o DNA mitocondrial é reconhecido pelo TLR-9, enquanto as histonas são reconhecidas pelos NLRs. Um DAMP chamado *high-mobility group box 1* (HMGB1) derivado do núcleo celular é reconhecido por TLRs (TLR-2 e TLR-4). Logo, os diferentes DAMPs apresentam receptores específicos (ROH; SOHN, 2018).

Fulop *et al*. (2017) sugeriram que, similar aos idosos, as PVHIV apresentam um estado de senescência celular, que colabora para manutenção da ISBG. Por exemplo, alguns antirretrovirais inibem proteínas responsáveis pela autofagia, um mecanismo importante relacionado a "limpeza" celular. Além disso, os antirretrovirais favorecem danos mitocondriais e nucleares, maximizando a circulação dos DAMPs, como o DNA mitocondrial e o HMGB1 (FULOP; HERBEIN; COSSARIZZA; WITKOWSKI *et al.*, 2017).

Korencak *et al*. (2019) verificaram aumento de DNA mitocondrial no citoplasma de linfócitos T $CD4^+$ em PVHIV que utilizam raltegravir e DTG. Esta alteração nos linfócitos também está associada à piora da eficiência oxidativa, maximizando a produção de EROs (KORENCAK; BYRNE; RICHTER; SCHULTZ *et al.*, 2019). As EROs podem ser reconhecidas pelo NLRP3, ativar o inflamassoma e aumentar a produção de citocinas inflamatórias (SWANSON; DENG; TING, 2019). Ainda, o próprio HIV e as suas proteínas acessórias são capazes de estimular o inflamassoma (JIN; ZHOU; HUANG, 2022; SWANSON; DENG; TING, 2019).

Recentemente, Drozd *et al*. (2016) verificaram um aumento de 1,95 ng/mL para 3,02 ng/mL de HMGB1 em PVHIV após 2 anos de carga viral indetectável. Este aumento foi verificado, sobretudo, em indivíduos que usaram esquemas terapêuticos com IP e INTR (DROZD; GRAHAM; CRANE; DELANEY *et al.*, 2016). Isso posto, a senescência celular parece ser uma importante contribuidora para a ISBG nas PVHIV e para antecipação do envelhecimento nesta população (COHEN; TORRES, 2017).

1.1.5.3 Inflamação metabólica

A inflamação metabólica, do inglês, *metainflammation*, é estimulada por diferentes origens. Como citado anteriormente, a desregulação da MI e do TA são importantes contribuintes para imunoativação e para ISBG.

A MI de adultos é composta, principalmente, pelos filos Firmicutes e Bacteroidetes e em menor proporção, pelos filos Actinobacteria, Proteobacteria e Verrucomicrobia. No que se

refere aos gêneros bacterianos, as *Bacteroides, Prevotella* e *Ruminococcus* parecem ser mais prevalentes (ECKBURG; BIK; BERNSTEIN; PURDOM *et al.*, 2005).

No envelhecimento, a MI exibe diferentes mudanças, em especial, a redução da diversidade bacteriana, com menor abundância de bactérias comensais, bactérias produtoras de butirato e a maior abundância de bactérias patobiontes. Embora a alimentação pareça ser um dos principais determinantes da composição da MI, o estudo de Claesson *et al*. (2012) revelou menor prevalência destes gêneros bacterianos em idosos (CLAESSON; JEFFERY; CONDE; POWER *et al.*, 2012). Além disso, foi verificado maior abundância de *Bacteroidetes* e *Proteobacteria*, acompanhada da redução de *Bifidobactéria* e *Lactobacilli* nos idosos (HE; OUWEHAND; ISOLAURI; HOSODA *et al.*, 2001; KONG; HUA; ZENG; NING *et al.*, 2016; O'TOOLE; JEFFERY, 2015).

Estas alterações parecem justificar a menor disponibilidade dos AGCCs, butirato proprionato e acetato, produzidos a partir da fermentação dos carboidratos acessíveis à microbiota intestinal (CORREA-OLIVEIRA; FACHI; VIEIRA; SATO *et al.*, 2016). A menor disponibilidade de AGCCs reduz a oferta energética para bactérias comensais, células imunológicas e para os colonócitos, bem como reduz a camada de muco. Em conjunto, estes mecanismos levam à alterações intestinais que maximizam o ambiente inflamatório (RAGONNAUD; BIRAGYN, 2021). Por exemplo, a menor camada de muco e o aumento da permeabilidade intestinal favorecem a translocação do LPS à corrente sanguínea. Acredita-se ainda, que a MI de idosos apresenta menor abundância de uma bactéria chamada *Akkermansia muciniphila*, que é responsável pela produção de muco. A abundância relativa de bactérias comensais está reduzida no envelhecimento, haja vista que as bactérias produtoras de butirato (I. *butyriciproducens*, F. *prausnitzii*, R. *faecis*, e A. *butyraticus*) estão reduzidas no intestino de idosos o que, além de reduzir função de barreira, leva à menor inibição do TLR-4 mediada por butirato. Estes dois mecanismos aumentam a possibilidade da via LPS-TLR-4 estimular o processo inflamatório (BACHEM; MAKHLOUF; BINGER; DE SOUZA *et al.*, 2019; RAGONNAUD; BIRAGYN, 2021).

O TLR-4 é um dos principais receptores de membrana que reconhece as moléculas capazes de estimular a produção de citocinas inflamatórias (LU; YEH; OHASHI, 2008). Em situações de maior permeabilidade intestinal, como no envelhecimento, o LPS interage com as células (p. ex., macrófagos) e os tecidos (p.ex., TA e ME) que expressam o TLR-4. Esta interação é dependente do CD14 e da LPB. A LPB, por exemplo, facilita a interação entre o LPS e o CD14, enquanto o CD14 possibilita a transferência do LPS ao TLR-4. O LPS é

composto por três partes, o lipídeo A, uma estrutura de oligossacarídeo e a cadeia lateral O. O lipídeo A do LPS é a principal responsável por estimular o TLR-4. O TLR-4 apresenta proteínas que permitem a transdução do sinal para dentro da célula, o *Toll-interleukin-1 receptor* (TIR) é o responsável por ativar proteínas que continuarão a sinalização intracelular, neste caso, a *myeloid differentiation primary response gene 88* (MyD88) (LU; YEH; OHASHI, 2008). A MyD88, por sua vez, ativa diferentes proteínas, como a *IL-1 receptor-associated kinase-4* (IRAK-4) e *TNF receptor-associated factor 6* (TRAF6). Essas proteínas convergem na ativação do *transforming growth factor-β-activated kinase* (TAK1) que, em seguida, ativa a IκB quinase. Especificamente, o complexo das IKKα, IKKβ e IKKγ fosforilam a IκB quinase, cuja função é impedir a continuidade da via. Contudo, a fosforilação da IκB quinase o inibe e o direciona para degradação, permitindo a translocação do NF-κB para o núcleo da célula. O NF-κB é responsável pelo aumento da expressão gênica e pela produção de citocinas inflamatórias (LU; YEH; OHASHI, 2008). Células mieloides como eritrócitos, granulócitos e macrófagos, e linfoides como linfócitos T e B e DC expressam TLR-4. Além disso, o TA e o ME também expressam TLR-4 (MCKERNAN; VARGHESE; PATEL; SINGER, 2020). Portanto, todas estas células e tecidos podem produzir citocinas inflamatórias e, por isso, o intestino se destaca como um importante contribuidor da ISBG. A **Figura 5** ilustra em detalhes a via inflamatória mediada pelo LPS, tendo em vista sua importante contribuição na imunoativação persistente e ISBG.

Os AGCCs também são fontes de energia para os linfócitos T, via β-oxidação, bem como atuam via receptores específicos de superfície (p. ex., GPR109A, GPR41, GPR43) que estão expressos na superfície de macrófagos, DC e neutrófilos. Especificamente o butirato, ao estimular estes receptores nestas células, induz a produção de citocinas anti-inflamatórias (BACHEM; MAKHLOUF; BINGER; DE SOUZA *et al.*, 2019). Portanto, a menor disponibilidade de AGCCs em idosos leva ao desequilíbrio da atividade das células imunológicas e maior circulação de mediadores inflamatórios. Por fim, as *Bifidobacterium*, também parecem estar reduzidas em idosos, estas contribuem para produção de lactato e AGCCs, os quais reduzem a abundância de bactérias que colaboram para instalação de um ambiente inflamatório (SELA; CHAPMAN; ADEUYA; KIM *et al.*, 2008).

Alterações na composição bacteriana intestinal das PVHIV estão sendo cada vez mais descritas (RUSSO; NANNINI; STERRANTINO; KIROS *et al.*, 2022). No estudo de Amador-Lara *et al*. (2022) com PVHIV, os autores observaram uma menor alfa diversidade, maior abundância de *Enterobacteriaceae* e *Prevotella*, bem como menor abundância de *Akkermansia*

Muciniphila e *Lactobacillus*, similar aos idosos (AMADOR-LARA; ANDRADE-VILLANUEVA; VEGA-MAGANA; PENA-RODRIGUEZ *et al.*, 2022).

Nesse cenário, um recente estudo avaliou o efeito da suplementação de butirato em macacos tratados com antirretroviral infectados com o vírus da imunodeficiência símia (SIV), equivalente ao HIV em humanos. Os autores hipotetizaram que a suplementação de butirato poderia colaborar para as mudanças intestinais e, por conseguinte, menor imunoativação e, por conseguinte, menor estado inflamatório. Contudo, os resultados do estudo revelaram que a suplementação de butirato não foi capaz de modificar os marcadores avaliados, como a contagem de linfócitos T $CD4^+$, a funcionalidade das células T, ativação imunológica e translocação bacteriana (ORTIZ; SIMPSON; LANGNER; BAKER *et al.*, 2022). Por outro lado, um estudo conduzido com humanos verificou efeitos positivos da suplementação de proprionato em PVHIV. Os autores observaram redução das citocinas inflamatórias, e menor quantidade de linfócitos T $CD8^+$ após 12 semanas de intervenção. Contudo, este estudo não foi randomizado e não contou com um grupo controle, o que limita a extrapolação dos resultados (BRAUCKMANN; NAMBIAR; POTTHOFF; HOXTERMANN *et al.*, 2022).

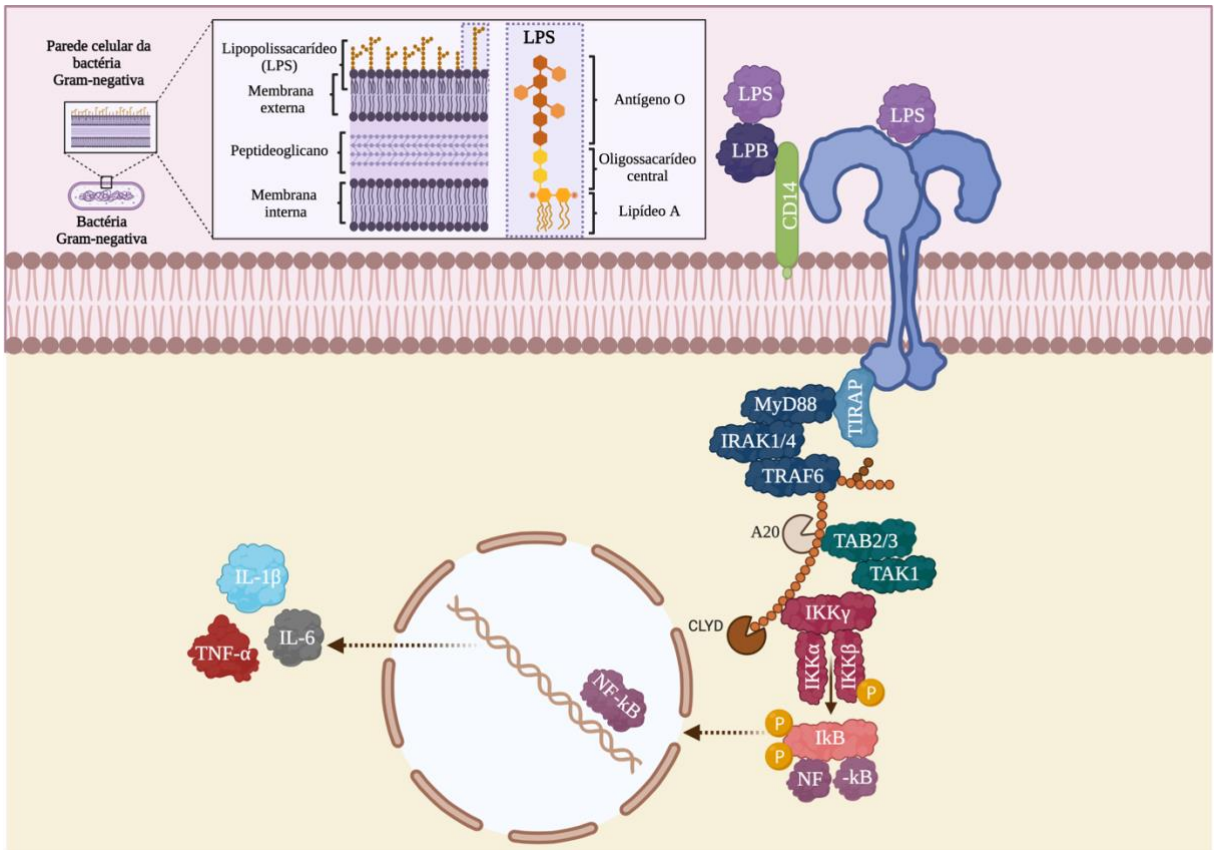

Figura 5. Inflamação mediada pelo lipopolissacarídeo. Lipopolissacarídeo (LPS), proteína ligadora lipopolissacarídeo (LPP), cluster de diferenciação 14 (CD14), *myeloid differentiation primary response gene 88* (MyD88), *IL-1 receptor-associated kinase-4* (IRAK4), *TNF receptor-associated factor 6* (TRAF6), TNF-α-induced protein 3 (A20), TGF-Beta Activated Kinase 1 (TAB2), *transforming growth factor-β-activated kinase*

(TAK1), IkappaB kinase (IKK), fator nuclear kappa B (NF-κB), interleucina-6 (IL-6), interleucina 1beta (IL-1β). Adaptado de (LU; YEH; OHASHI, 2008).

Ainda, no que se refere à inflamação metabólica, o papel do TA é amplamente estabelecido, principalmente, porque nos idosos, uma das principais alterações na composição corporal, é a redistribuição de gordura que, similar ao que acontece com as PVHIV que desenvolveram lipodistrofia, aumentam a quantidade de gordura visceral, com maior potencial inflamatório (KUK; SAUNDERS; DAVIDSON; ROSS, 2009). Como citado anteriormente, a desregulação do TA leva ao aumento de AGL circulantes, maior quimiotaxia de monócitos e diferenciação de macrófagos, em especial, do subtipo M1. Além disso, a desregulação do TA favorece a resistência à insulina local e periférica e a ativação do NLRP3 inflamassoma. O TA também apresenta em sua superfície os receptores TLR-4 e TLR-2, que se ativam em resposta ao LPS e aos AGL, respectivamente (REILLY; SALTIEL, 2017). Ademais, no envelhecimento, o TA apresenta células senescentes que contribuem para ativação de vias inflamatórias. Por exemplo, as células senescentes no TA aumentam a quimiotaxia de monócitos que se diferenciam em macrófagos (do subtipo M1) e estimulam vias inflamatórias (OU; ZHANG; TAN; ZHOU *et al.*, 2022). Ainda, uma importante desregulação do TA no envelhecimento é a menor adipogênese. No envelhecimento as células progenitoras de adipócitos diminuem e isso se deve à redução dos genes pró-adipogênicos como C/EBPα e PPARγ. A menor adipogênese contribui para o aumento da hipertrofia dos adipócitos e, por conseguinte, o desencadeamento de vias inflamatórias locais e sistêmicas (OU; ZHANG; TAN; ZHOU *et al.*, 2022). Em conjunto, estas alterações levam à lipotoxicidade e ao acúmulo ectópico de gordura (OU; ZHANG; TAN; ZHOU *et al.*, 2022).

Nas PVHIV, as proteínas acessórias do vírus contribuem para o fenótipo senescente do TA, culminando em menor adipogênese e maior hipertrofia dos adipócitos (GORWOOD; EJLALMANESH; BOURGEOIS; MANTECON *et al.*, 2020). Ainda, estas proteínas acessórias do HIV estão associadas a maior circulação de citocinas inflamatórias (GORWOOD; EJLALMANESH; BOURGEOIS; MANTECON *et al.*, 2020). A **Figura 6** ilustra as vias que medeiam a inflamação no TA, bem como o papel do HIV e das suas proteínas acessórias.

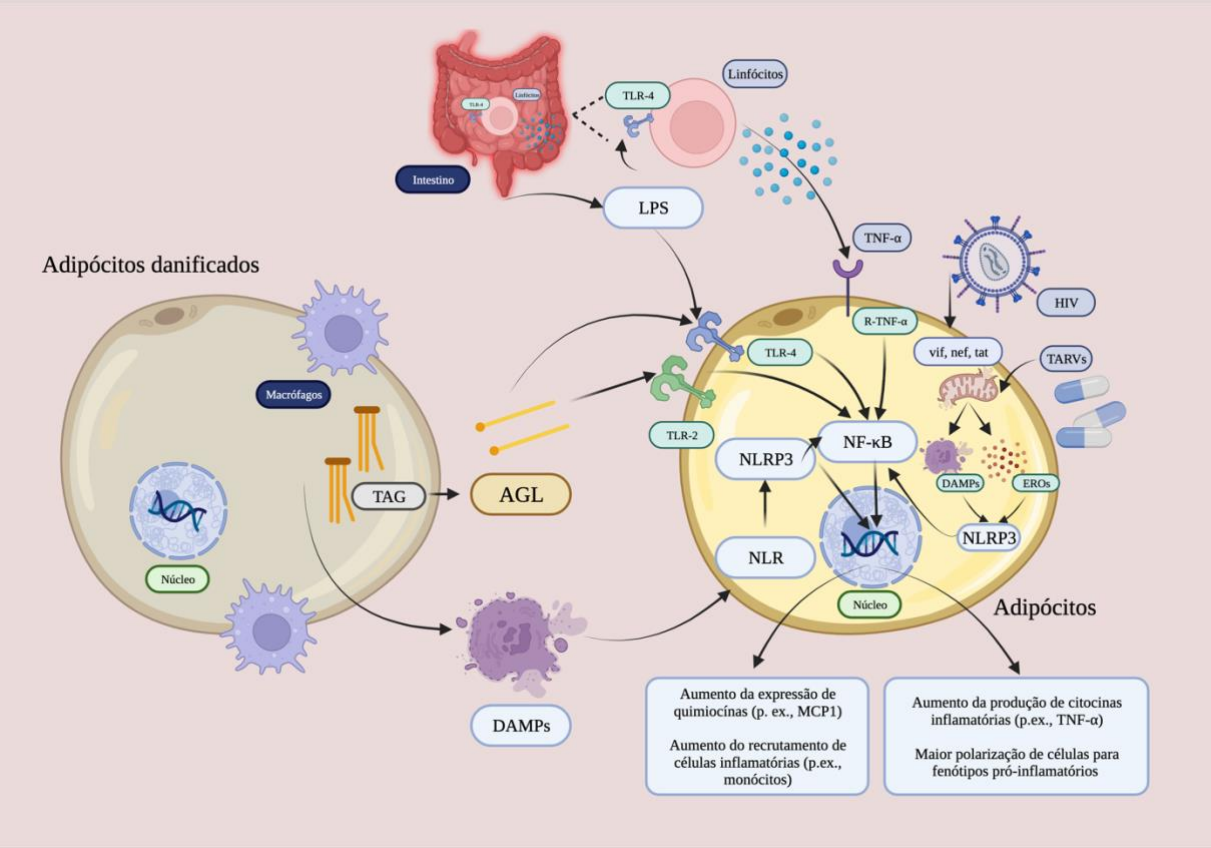

Figura 6. Vias que medeiam o processo inflamatório no tecido adiposo. Legenda: Triacilglicerol (TAG), ácidos graxos livres (AGL), padrões moleculares associados a danos (DAMPs), *Toll-like receptor 2* (TLR-2), *toll-like receptor 4* (TLR-4), lipopolissacarídeo (LPS), fator de necrose tumoral alfa (TNF-α), receptor de TNF-α (R-TNF-α), vírus da imunodeficiência humana (HIV), *virion infectivity factor* (vif), *negative factor* (nef), *trans-activator of transcription* (tat), terapia antirretroviral (TARV), espécies reativas ao oxigênio (EROs), *Nod-like receptor* (NLR), *NLR proteins 3* (NLRP3), fator nuclear kappa B (NF-κB), proteína de quimiotaxia 1 (MCP1). Adaptado e traduzido de KOETHE; LAGATHU; LAKE; DOMINGO *et al.* (2020); REILLY e SALTIEL (2017).

Finalmente, outro contribuinte é a alimentação. O excesso de nutrientes, especialmente, derivados de carboidratos de rápida resposta glicêmica, como dissacarídeos (p. ex., sacarose) e monossacarídeos (p. ex., glicose) e ácidos graxos, em especial, saturados, são capazes de estimular o TLR-4 em macrófagos e contribuir para o aumento da expressão gênica de citocinas inflamatórias. Os macrófagos possuem transportadores de glicose (GLUT-1) e de ácidos graxos (CD-36), e o aumento da captação destes substratos, principalmente quando a ingestão energética é elevada frente ao gasto energético (balanço energético positivo), faz com que os macrófagos fiquem hiperestimulados (SHAPIRO; LUTATY; ARIEL, 2011). Ainda sobre a alimentação, a dieta ocidental, favorece a estimulação desregulada dos linfócitos T $CD8^{+}$, das células NK e das células linfoides inatas que colaboram para ativação de macrófagos e a sua

diferenciação para o fenótipo M1 (SCHEITHAUER; RAMPANELLI; NIEUWDORP; VALLANCE *et al.*, 2020).

Conforme descrito acima, diversas similaridades entre as PVHIV e os idosos reforçam a hipótese do envelhecimento antecipado e, por isso, é esperado que as alterações que ocorrem com os idosos, aconteçam antecipadamente nas PVHIV.

1.1.6 Inflamação sistêmica como fator etiológico para sarcopenia em PVHIV

Em uma revisão sistemática publicada por Cabrera *et al*. (2021), composta apenas por estudos publicados na América Latina, sendo 79% estudos brasileiros, foi observado que envelhecer com HIV aumenta a probabilidade de desenvolver diferentes condições (p. ex., síndrome metabólica, hipertensão arterial sistêmica, desordens cerebrais, dislipidemia, doenças ósseas etc.), sobretudo doenças cardiovasculares, reforçando que as PVHIV, atualmente, apresentam maior probabilidade de morrer por doenças não-AIDS, como as doenças crônicas. Além disso, neste estudo, verificaram que envelhecer com HIV está associado a diversos comprometimentos físicos e funcionais que impactam negativamente na qualidade de vida (CABRERA; DIAZ; GRIMSHAW; SALVATIERRA *et al.*, 2021). Logo, o desenvolvimento das doenças não-AIDS tem sido cada vez mais observado em PVHIV, uma vez que o número de pessoas mais velhas com HIV aumenta significativamente.

Dentre as doenças não-AIDS, destaca-se a sarcopenia, uma doença músculo esquelética caracterizada pela redução da força (dinapenia), massa e da função muscular. A sarcopenia possui etiologia complexa e dinâmica, e diversos fatores interatuam para sua gênese. No que tange os fatores associados à sarcopenia, despontam a inatividade física, que inclui comportamentos predominantemente sedentários (p. ex., ficar sentado e não subir escadas), assim como não realizar exercícios físicos específicos (p. ex., treino de força) (IZQUIERDO; MERCHANT; MORLEY; ANKER *et al.*, 2021). Ainda, a alimentação inadequada (p. ex., menor consumo energético, proteico e de micronutrientes) (SANTIAGO; RORIZ; RAMOS; FERREIRA *et al.*, 2021), as doenças crônicas (p. ex., diabetes mellitus e dislipidemia) (FENG; GAO; HU; WU *et al.*, 2021), as doenças respiratórias (SEPULVEDA-LOYOLA; OSADNIK; PHU; MORITA *et al.*, 2020), as doenças cardiovasculares (HE; ZHANG; ZHANG; ZHANG *et al.*, 2021) e a polifarmácia (PANA; SOURTZI; KALOKAIRINOU; VELONAKI, 2022) fazem parte da complexa etiologia da sarcopenia. Ademais, outros fatores como o tabagismo e a má qualidade do sono também fazem parte da matriz de fatores que levam à sarcopenia (GAO;

HU; YAN; ZHAO *et al.*, 2021). Finalmente, as alterações na atividade neural e a perda de neurônios alfa motores estão associadas, especialmente, à redução da força muscular (dinapenia), importante componente da sarcopenia (RUIZ, 2022).

A sarcopenia pode ser categorizada em primária e secundária. A sarcopenia primária é causada exclusivamente pela idade, sem outras causas evidentes, enquanto a sarcopenia secundária, pode estar associada a outras doenças e condições (CRUZ-JENTOFT; BAEYENS; BAUER; BOIRIE *et al.*, 2010). Neste caso, é possível que as PVHIV, via ISBG, que também é uma característica do envelhecimento, estejam mais suscetíveis ao desenvolvimento da sarcopenia, principalmente porque o músculo esquelético (ME) é amplamente responsivo a mediadores inflamatórios (BANO; TREVISAN; CARRARO; SOLMI *et al.*, 2017; DALLE; ROSSMEISLOVA; KOPPO, 2017; LYNCH; MURPHY; CASTRO; ROCHE, 2020; TUTTLE; THANG; MAIER, 2020).

O ME desempenha importantes funções no organismo humano, tais como manutenção da postura, locomoção, movimentação de objetos, independência física e regulação metabólica, haja vista sua participação na homeostase das principais biomoléculas energéticas (p. ex., glicose, ácidos graxos e aminoácidos) (BASKIN; WINDERS; OLSON, 2015). O ME também é responsável pela liberação de moléculas chamadas de miocinas, cujas ações podem acontecer no próprio ME, bem como em outros tecidos (BASKIN; WINDERS; OLSON, 2015). Ainda, o reconhecimento da importância do ME à saúde humana se deve, ao menos em parte, a compreensão de que a qualidade muscular – definida por aspectos morfológicos, fisiológicos, bioquímicos e mecânicos – é um importante preditor da qualidade de vida e da mortalidade (LIM; FRONTERA, 2022; WANG; YAO; ZIREK; REIJNIERSE *et al.*, 2020).

A manutenção do ME se dá a partir de um equilíbrio dinâmico e complexo, entre a síntese e a degradação de proteínas, frequentemente chamado de balanço proteico muscular. A síntese proteica muscular (SPM) é regulada por diferentes fatores, tais como hormônios (p. ex., IGF-1 e insulina), nutrientes (p. ex., aminoácidos), estímulo mecânico (p. ex., exercício físico de força) e o estado inflamatório (p. ex., doenças) (NAIR; SCHWENK, 1994). Estes fatores são capazes de ativar ou inibir uma proteína chamada Mecanismo Alvo da Rapamicina (mTOR). Essa proteína é ativada a partir da fosforilação da PI3-K e da proteína quinase B (Akt ou PKB); logo, a via PI3-3/AKT/mTOR é uma das vias mais estudadas e, possivelmente, uma das mais importantes e responsáveis pela SPM. Após a ativação da mTOR, os complexos proteicos mTORC1 e mTORC2 são acionados, no entanto, o complexo mTORC1 é o principal responsável pela SPM. Essa via é estimulada, principalmente, pela insulina e pelo IGF-1, assim

como é influenciada por citocinas, nutrientes, e pelo *status* energético celular. A ativação do complexo mTORC1 estimula positivamente a proteína ribossomal S6 (p70S6K1) e negativamente a 4E proteína de ligação 1 (4EBP1). Simultaneamente, a ativação do complexo mTORC1 inibe as proteínas que regulam as vias de degradação proteica, tais como: (i) autofagia lisossomal e (ii) ubiquitina proteassoma, que são cruciais no processo de atrofia muscular (SARTORI; ROMANELLO; SANDRI, 2021). Por outro lado, o catabolismo proteico muscular (CPM) é mediado por fatores de transcrição que regulam a atrofia muscular, chamados de FoxOs-atrogenes. As proteínas FoxO regulam os fatores de transcrição que inibem a via IGF-1/Insulina - PI3-K/AKT/mTOR e ativam mediadores que estimulam o CPM (SARTORI; ROMANELLO; SANDRI, 2021). A **Figura 7** ilustra as vias de SPM e COM.

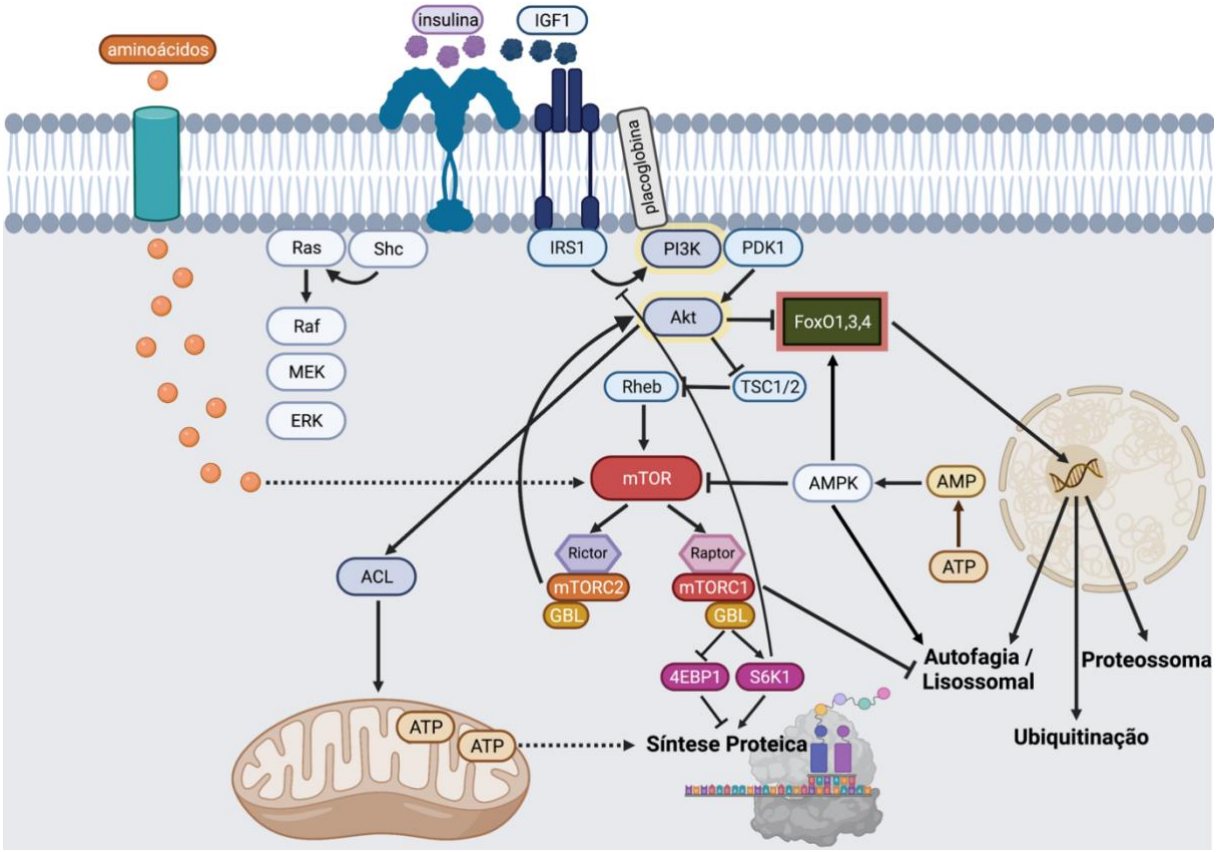

Figura 7. Vias moleculares responsáveis pelo balanço proteico muscular. Legenda: IGF-1 – fator de crescimento semelhante à insulina; IRS-1 – substrato do receptor de insulina; PI3-K – fosfoinositol-3-quinase; PDK1 – piruvato desidrogenase quinase 1; AKT – proteína quinase B; mTOR – mecanismo alvo da rapamicina; mTORC1 – complexo do mecanismo alvo da rapamicina 1; ATP – adenosina trifosfato; AMP = adenosina monofosfato; AMPK – adenosina monofosfato quinase; Ras – *rat sarcoma virus*; RAF - *Rapidly Accelerated Fibrosarcoma*; MEK ou MAPK ou ERK - *Mitogen-activated protein kinase kinase*; Rheb - *Ras homolog enriched in brain*; TSC1/2 - *Tuberous sclerosis proteins 1* e *2*, ou TSC1 (*hamartin*) e TSC2 (*tuberin*); Raptor - *Regulatory-associated protein of mTOR*; 4EBP1 - *eukaryotic translation initiation factor 4E binding protein 1*; S6K1 - *p70 ribosomal S6 kinase 1*. A imagem ilustra o papel dos aminoácidos, da insulina e do IGF-1 sobre a SPM. Os três estímulos

aumentam o ambiente anabólico por meio de diferentes vias de sinalização que convergem na ativação do complexo mTORC1. Traduzido e adaptado de SARTORI; ROMANELLO e SANDRI (2021).

Levando em consideração que a ISBG consiste em um importante pilar par as alterações musculares, as mudanças citadas anteriormente que levam à imunoativação e ao aumento de mediadores inflamatórios (p. ex., IL-6, TNF-α, LPS, NF-κB), estão potencialmente relacionadas às alterações no estado muscular. Por exemplo, recentemente, uma revisão sistemática com meta-análise que compilou os resultados de 168 estudos (149 estudos transversais e 19 longitudinais) contando com 12, 295 participantes, revelou que os elevados níveis de IL-6, proteína C reativa (PCR) e de TNF-α, foram associados a menor força e massa muscular, componentes da sarcopenia (TUTTLE; THANG; MAIER, 2020).

A **Figura 8** ilustra o papel destes diferentes mediadores inflamatórios nas alterações musculares. Estas alterações, que em grande medida, são similares as que ocorrem no TA afetam o ME, deflagrando vias inflamatórias (p. ex., NF-κB) capazes de promover a resistência à insulina e ativar proteínas das vias ubiquitina proteassoma e autofagia lisossomal, estimuladas pela FoxO (MUKUND; SUBRAMANIAM, 2020; SARTORI; ROMANELLO; SANDRI, 2021). Além disso, as próprias citocinas inflamatórias, ao estimularem os seus respectivos receptores encontrados no ME, são capazes de maximizar vias catabólicas. Ainda, o ME apresenta o TLR-4, que pode ser estimulado pelo LPS, derivado do intestino, e pelos AGL, advindos do TA que, quando desregulados, ficam em elevadas concentrações na corrente sanguínea. Ambos, LPS e AGL, estimulam vias inflamatórias no ME capazes de deflagrar vias catabólicas (HARAN; RIVAS; FIELDING, 2012). Ademais, estes AGL oriundos do TA poderiam infiltrar no ME e gerar um quadro de lipotoxicidade, resistência à insulina e anabólica. Alguns estudos observaram que as PVHIV apresentaram uma menor densidade muscular, sobretudo pelo aumento do conteúdo de triacilglicerol intramuscular (ADRIAN; MIAO; FENG; SCHERZINGER *et al.*, 2020; KOUSARI; MOSER; OLEFSKY; BROWN *et al.*, 2021; NATSAG; ERLANDSON; SELLMEYER; HABERLEN *et al.*, 2017), reforçando as hipóteses acerca das alterações do TA impactarem a qualidade muscular do ME das PVHIV.

Mecanismos mais recentes, também associados ao intestino e à MI, poderiam explicar, ao menos em parte, as alterações negativas no ME. Por exemplo, o ME apresenta receptores (p. ex., GPR41 e GPR43) de AGCCs. Ao estimular estes receptores, os AGCCs aumentam a eficiência oxidativa do ME e diminuem o acúmulo de lipídeos intramusculares, relacionados a resistência à insulina, lipotoxicidade e resistência anabólica (CRAKES; JIANG, 2019;

FRAMPTON; MURPHY; FROST; CHAMBERS, 2020). Além disso, os AGCC são cruciais para o controle da permeabilidade intestinal, evitando a translocação do LPS ao GALT e à corrente sanguínea (CRAKES; JIANG, 2019). Contudo, como citado anteriormente, PVHIV apresentam alterações intestinais que levam à menor produção de AGCCs.

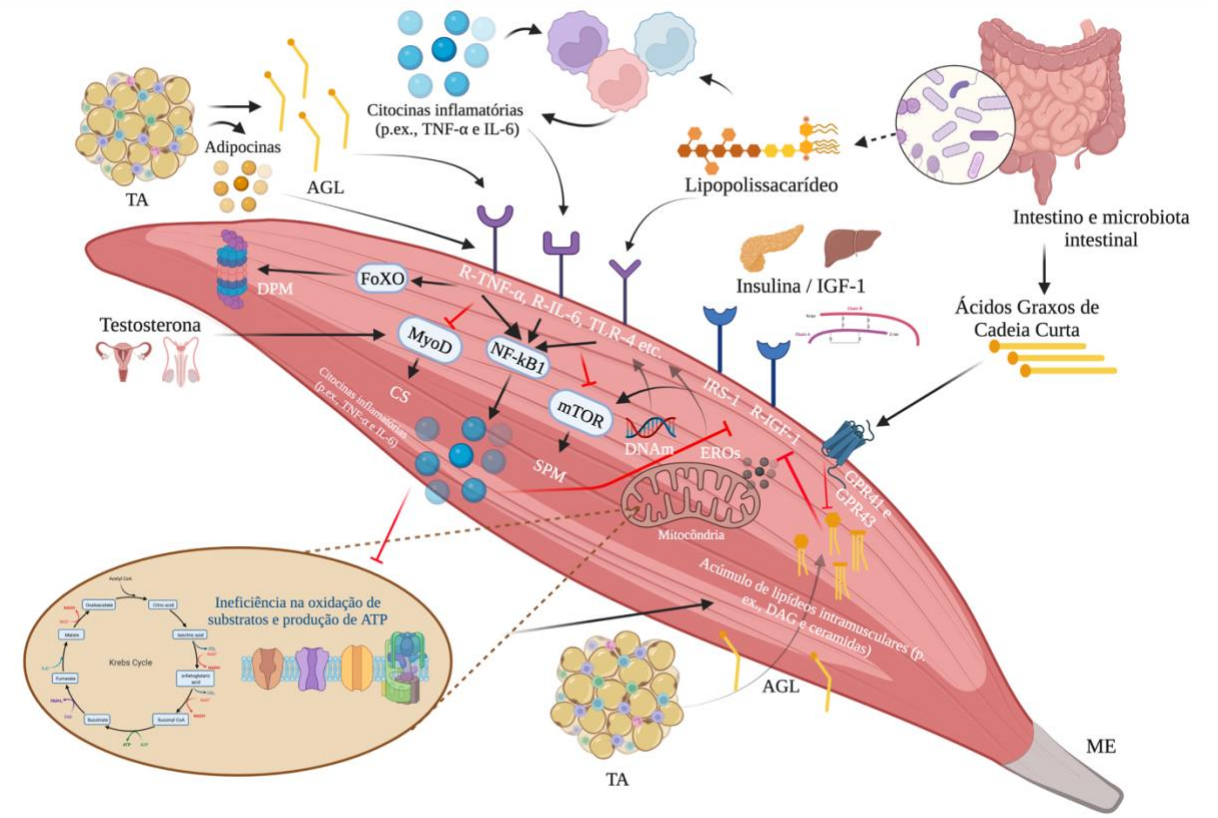

Figura 8. Mediadores inflamatórios que afetam o estado muscular. Legenda: tecido adiposo (TA), ácidos graxos livres (AGL), fator de necrose tumoral alfa (TNF-α), interleucina-6 (IL-6), fator de crescimento semelhante à insulina 1 (IGF-1), degradação proteica muscular (DPM), forkhead box O (FOXO), myoblast determination protein 1 (MyOD), células satélites (CS), fator nuclear kappa B (NF-κB), mecanismo alvo da rapamicina (mTOR), síntese proteica muscular (SPM), ácido ribonucleico mitocondrial (DNAm), espécies reativas ao oxigênio (EROs), diacilglicerol (DAG), receptor de TNF-α (R- TNF-α), receptor de IL-6 (R-IL6), toll-like receptor 4 (TLR-4), substrato do receptor de insulina (IRS-1), receptor de IGF-1 (R-IGF-1), glicoproteína 41 (GPR41), glicoproteína 43 (GPR43), músculo esquelético (ME). Adaptado de LYNCH; MURPHY; CASTRO e ROCHE (2020).

1.1.7 Avaliação da sarcopenia em pessoas vivendo com HIV

Em 1989, Irwin Rosenberg, cunhou o termo "Sarcopenia". O significado de sarcopenia deriva das palavras gregas "*sarx*" que significa músculo e "*penia*" que significa perda; portanto, perda de músculo (ROSENBERG, 1997). Desde a sua concepção, foram feitos questionamentos sobre os fatores etiológicos e os desdobramentos da sarcopenia na saúde humana. Nesse sentido, ao longo dos anos, pesquisadores da área descobriram novas

características relacionadas a sarcopenia (CRUZ-JENTOFT; SAYER, 2019), incluindo o papel da ISBG na sua gênese (DALLE; ROSSMEISLOVA; KOPPO, 2017; LIVSHITS; KALINKOVICH, 2019; WANG, 2022).

Por muito tempo a sarcopenia foi considerada apenas a redução da massa muscular (MM), com poucas referências à força muscular (CRUZ-JENTOFT; SAYER, 2019). Atualmente, a sarcopenia é definida pela redução de ambos, força muscular (dinapenia) e da MM, podendo se manifestar em diferentes graus de severidade. Em 2016, a sarcopenia foi reconhecida como uma doença muscular e inserida na Classificação Internacional de Doenças (CID), tendo como código CID-10M62.84 (ANKER; MORLEY; VON HAEHLING, 2016; CAO; MORLEY, 2016). O *European Working Group on Sarcopenia in Older People* (EWGSOP) publicou em 2019 o mais recente e utilizado consenso para definição de sarcopenia (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019). Apesar do consenso europeu ser o mais utilizado, é importante destacar que existem outros grupos, de países diferentes, que publicaram consensos ou posicionamentos para determinar a sarcopenia (BAUER; MORLEY; SCHOLS; FERRUCCI *et al.*, 2019; BHASIN; TRAVISON; MANINI; PATEL *et al.*, 2020; CHEN; WOO; ASSANTACHAI; AUYEUNG *et al.*, 2020; DENT; MORLEY; CRUZ-JENTOFT; ARAI *et al.*, 2018).

O EWGSOP (2019) propõe um algoritmo para rastreio, avaliação e determinação da severidade da sarcopenia. Por exemplo, na etapa de rastreio se utiliza questionários ou a avaliação clínica. Em seguida, para determinação de provável sarcopenia se avalia a força muscular que, se for menor que o ponto de corte estabelecido, deve ser prosseguido para avaliação da MM. Finalmente, a severidade da sarcopenia será estabelecida com testes de desempenho físico (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019) A **Figura 9** ilustra o algoritmo proposto para definição de sarcopenia segundo o EWGSOP 2019. Abaixo, cada uma destas etapas será detalhada.

1.1.7.1 Rastreio de sarcopenia

O rastreio de sarcopenia pode ser feito com questionários e por análise clínica. O questionário mais utilizado é o SARC-F (acrônimo de força, assistência ao caminhar, levantar-se de uma cadeira, subir escadas e quedas) (MALMSTROM; MILLER; SIMONSICK; FERRUCCI *et al.*, 2016; MALMSTROM; MORLEY, 2013). Originalmente, o SARC-F foi desenvolvido para ser uma ferramenta de rápido diagnóstico de sarcopenia e, atualmente, tem sido usado como uma ferramenta de rastreio. As perguntas do SARC-F são feitas com base em

alterações clínicas associadas ao ME, sendo: (i) O quanto de dificuldade você tem para levantar e carregar 5 kg?; (ii) O quanto de dificuldade você tem para atravessar um cômodo?; (iii) O quanto de dificuldade você tem para levantar de uma cama ou cadeira?; (iv) O quanto de dificuldade você tem para subir um lance de escadas de 10 degraus?; (v) quantas vezes você caiu no último ano? Para cada componente, 0 significa melhor condição e 2 significa pior condição. A somatória total permite uma pontuação de 10 pontos. O resultado do SARC-F se apresenta de forma dicotômica. Pontuações entre 0 e 3 define-se como "sem risco de sarcopenia" e a pontuação ≥ 4 define-se como "com risco de sarcopenia". Caso os avaliados não pontuem positivamente para risco de sarcopenia, não se deve, segundo o algoritmo, continuar a avaliação. O EWGSOP sugere repetir a avaliação após 6-12 meses para checar potenciais mudanças no quadro (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019).

1.1.7.2 Avaliação da força muscular

A força muscular é avaliada, principalmente, por meio de um equipamento chamado dinamômetro, que mensura a força de preensão manual (FPM) ou força de preensão palmar (FPP) tratados a partir de agora como FPP por serem sinônimos (ROBERTS; DENISON; MARTIN; PATEL *et al.*, 2011). É importante destacar que a avaliação por meio do dinamômetro não é exclusiva e outros métodos podem ser utilizados como, por exemplo, o teste de "sentar e levantar", que geralmente conta com auxílio de uma cadeira, sendo contabilizado o número de repetições em um determinado período (PINHEIRO; CARNEIRO; COQUEIRO; PEREIRA *et al.*, 2016). Tendo em vista a ampla utilização do dinamômetro na análise de força muscular no cenário do envelhecimento, dinapenia e sarcopenia, vamos detalhar a utilização desse método.

O dinamômetro é uma ferramenta que avalia a força muscular pico ou máxima de membro superior e o tipo de força avaliada é a isométrica (MCGRATH; TOMKINSON; CLARK; CAWTHON *et al.*, 2021). A FPP máxima consiste em um teste simples, seguro e confiável para mensurar a função muscular e, além disso, estudos anteriores mostraram que a menor FPP foi associada a condições negativas relacionadas à idade e doenças (p. ex., doença cardiovascular, demência, incapacidade física etc.) (LEONG; TEO; RANGARAJAN; LOPEZ-JARAMILLO *et al.*, 2015). Entretanto, apesar de ser um teste bem estabelecido, com base nos dados disponíveis na literatura, algumas limitações podem ser apontadas no que tange a função muscular como, por exemplo, a incapacidade do teste de extrapolar a força muscular para todos

os grupamentos musculares e a pluralidade do conceito de força muscular que, por sua vez, vai além da força máxima (MCGRATH; TOMKINSON; CLARK; CAWTHON *et al.*, 2021).

Conforme citado anteriormente, a força muscular foi considerada um parâmetro mais relevante para o diagnóstico de sarcopenia, haja vista que essa variável é considerada um preditor mais adequado para desfechos negativos. Por exemplo, no estudo de coorte (seguimento médio de 7 anos) publicado por Celis-Morales *et al*. (2018), que contou com 502, 293 mil participantes (40 – 69 anos de idade) da Inglaterra, País de Gales e Escócia, foi observado – após controlar por diversas variáveis confundidoras (p. ex., idade, etnia, nível socioeconômico, tabagismo, realização de exercícios físicos, comportamento sedentário, consumo de vegetais, frutas, peixe carne vermelha e processada etc.) – que a redução da força muscular (~ 5 kg) foi associada a maior incidência e mortalidade por doenças respiratórias e diversos tipos de câncer. Além disso, a redução da força muscular aumentou a incidência de doenças cardiovasculares em mulheres (1,15; 95% IC 1,13 – 1,17; p< 0,001) e homens (1,11; 95% IC 1,10 – 1,12; p< 0,001). Igualmente, foi observado aumento do risco de mortalidade por doenças cardiovasculares em mulheres (1,20; 95% IC 1,17 – 1,23; p< 0,001) e homens (1,16; 95% IC 1,15 – 1,17; p< 0,001). Para os outros desfechos, resultados similares foram identificados, reforçando que a força muscular é um preditor importante para desfechos negativos em saúde (CELIS-MORALES; WELSH; LYALL; STEELL *et al.*, 2018). Estes achados vão ao encontro de outros estudos publicados, enaltecendo a importância da avaliação da força muscular, sobretudo por ser um método simples e menos dispendioso (HO; CELIS-MORALES; PETERMANN-ROCHA; SILLARS *et al.*, 2019; LEONG; TEO; RANGARAJAN; LOPEZ-JARAMILLO *et al.*, 2015; LIU; CHEN; SONG; WANG *et al.*, 2021).

1.1.7.3 Avaliação da massa muscular

A confirmação do diagnóstico de sarcopenia é feita a partir da mensuração da massa muscular apendicular (MMA), geralmente corrigida pela estatura ao quadrado (MMA/e^2). Nesse contexto, Heymsfield *et al*. (1990) propuseram a definição da MMA avaliada pelo DEXA (Lunar®). Para construção da definição da MMA, inicialmente os autores descreveram que as extremidades contemplam o esqueleto (conteúdo ósseo), a MM e a massa gorda (adiposidade). A respeito da massa óssea, os autores não consideraram a quantificação da medula, e no que se refere a MM, os autores assumiram a quantidade de pele e tecido subcutâneo intrínseco aos membros avaliados. Portanto, a MMA é definida pela massa total dos braços e pernas menos a

quantidade de gordura e a massa óssea desses membros (HEYMSFIELD; SMITH; AULET; BENSEN *et al.*, 1990).

Em 1997, Gallagher *et al.* a partir de dados derivados de Gallagher *et al.* (1996), avaliaram a MMA de 148 mulheres (80 afroamericanas e 68 caucasianas) e 136 homens (72 afroamericanos e 64 caucasianos) por meio da DEXA (Lunar®). Nesse estudo, os autores verificaram que a idade foi o principal preditor negativo da MMA, ao passo que a massa corporal e a estatura foram os principais preditores positivos. Ainda, os achados desses autores relevaram que ambos, homens e mulheres afrodescendentes, possuem mais MMA comparativamente aos caucasianos (GALLAGHER; VISSER; DE MEERSMAN; SEPULVEDA *et al.*, 1997). Com base nos resultados deste estudo, Baumgartner *et al.* (1998) propuseram o ponto de corte para definição de sarcopenia, sendo considerado valores menores (- 2 desvios padrão do grupo de referência cujas estratificações são feitas por sexo) do índice de MMA (IMMA) que é a MMA/e^2. Segundo esses autores, os valores do IMMA menores que 7,26 e 5,5 kg/m^2 para homens e mulheres, respectivamente, confirma-se a sarcopenia. Além disso, os achados deste estudo mostraram que a idade (> 75 anos) e uma pior condição socioeconômica foram os principais preditores positivos para sarcopenia (BAUMGARTNER; KOEHLER; GALLAGHER; ROMERO *et al.*, 1998). Cabe destacar que a definição proposta por Baumgartner *et al.* (1998) é amplamente utilizada isoladamente para definição de sarcopenia, mesmo após as publicações dos consensos de sarcopenia que inseriram a força muscular.

1.1.7.4 Severidade da sarcopenia

De acordo com os consensos atuais de sarcopenia, a avaliação do desempenho físico é fundamental para estabelecer a severidade desta doença. O quadro de sarcopenia severa é diagnosticado quando um indivíduo apresenta menor força e MM, bem como menor desempenho físico. Os testes propostos para avaliar o desempenho físico de acordo com o EWGSOP2 são: (i) velocidade de marcha; (ii) bateria curta de desempenho físico; (iii) teste de levantar-se e ir; (iv) teste de 400 m de caminhada. Todos os testes podem ser utilizados de acordo com as características dos indivíduos avaliados. O teste de velocidade de marcha é considerado o mais rápido, seguro e confiável para sarcopenia. Os resultados do teste mostraram ser bons preditores para diferentes desfechos negativos (p. ex., sarcopenia, prejuízo cognitivo, necessidade de institucionalização, quedas e mortalidade) (ABELLAN VAN KAN; ROLLAND; ANDRIEU; BAUER *et al.*, 2009).

Manualmente, com auxílio de um cronometro, mensura-se o tempo necessário para percorrer uma distância de 4 m, cuja velocidade de marcha aplicada deve ser habitual. Para idosos saudáveis a confiabilidades teste-reteste para distância de 4 m variou entre 0,96 – 0,98 (PETERS; FRITZ; KROTISH, 2013). Respectivamente, variações de 0,05 m/s e 0,1 m/s são consideradas potenciais e relevantes para mudanças clínicas (PERERA; MODY; WOODMAN; STUDENSKI, 2006). O ponto de corte estabelecido para esse teste é ≤ 0.8 m/s (KARPMAN; LEBRASSEUR; DEPEW; NOVOTNY *et al.*, 2014).

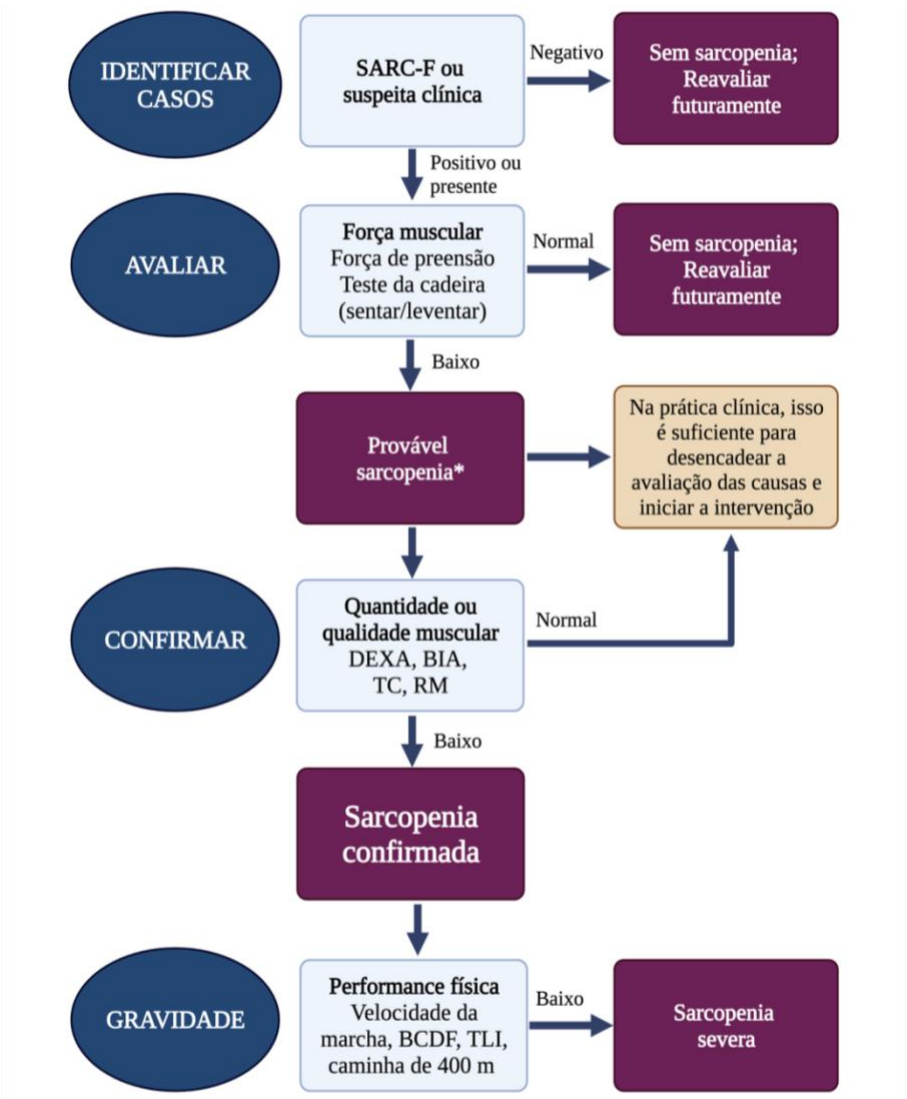

Figura 9. Algoritmo para definição de sarcopenia de acordo com EWGSOP2 (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019). Legenda: DEXA – absormetria de raios-x de dupla energia; BIA – bioimpedância elétrica; TC – tomografia computadorizada; RM – ressonância magnética; BRDF – bateria curta de rendimento físico; TLI – teste de levantar-se e ir; m – metros.

1.1.8 Sarcopenia em pessoas vivendo com HIV

Os estudos que avaliaram sarcopenia em PVHIV são heterogêneos, e consideraram majoritariamente apenas a redução da MM como parâmetro para definição de sarcopenia. Além disso, poucos estudos compararam a prevalência de sarcopenia entre um grupo de PVHIV e um grupo controle (DUTTA; GARGA; GADPAYLE; BANSAL *et al.*, 2018; DUTTA; SHARMA; BANSAL; SHARMA *et al.*, 2017; ERLANDSON; TRAVISON; ZHU; MAGAZINER *et al.*, 2020; HAWKINS; ZHANG; NG; ALTHOFF *et al.*, 2018; KRUGER; HAVEMANN-NEL; RAVYSE; MOSS *et al.*, 2016; MIALICH; DOS SANTOS; DA SILVA; DE PAULA *et al.*, 2017; PINTO NETO; SALES; SCARAMUSSA; DA PAZ *et al.*, 2016), dificultando a compreensão dos achados.

No estudo brasileiro publicado por Pinto Neto *et al*. (2016) os autores avaliaram 93 indivíduos, sendo 33 pessoas com HIV (90,9% com a carga viral indetectável), com idade variando entre 50 e 78 anos. No grupo controle, 60 pessoas foram avaliadas, com idade variando entre 60 e 87 anos. Tendo como base o critério europeu de 2010 para definição de sarcopenia, os autores observaram que no grupo controle 86,7, 6,7 e 6,77% foram considerados sem sarcopenia, com pré-sarcopenia e com sarcopenia, respectivamente. No grupo HIV o número de pessoas com pré-sarcopenia e sarcopenia foi maior, podendo se verificar que 63,6, 12,1 e 24,2% foram considerados sem sarcopenia, com pré-sarcopenia e com sarcopenia, respectivamente. Além disso, os autores verificaram que, quando controlado para idade e pelo índice de massa corporal (IMC), viver com HIV aumentava a chance de pré-sarcopenia em OR 3,9 (95% IC: 1,38 – 10,95) e sarcopenia em OR 5,20 (95% IC: 1,40 – 19,20). Outro estudo brasileiro publicado recentemente por Oliveira *et al*. (2021), que contou com 302 PVHIV (151 homens) com idade média de 51,7 anos, mostrou que a prevalência de sarcopenia foi de 4,1 e 1% considerando os critérios europeus para sarcopenia de 2010 e 2019, respectivamente (OLIVEIRA; BORSARI; CARDENAS; ALVES JUNIOR *et al.*, 2021).

Recentemente, Oliveira *et al*. (2020), ao considerar todos os estudos que avaliaram sarcopenia em PVHIV, observaram uma prevalência de 24,1% (95% IC: 17,8 – 31,0%). Esta prevalência foi maior utilizando apenas a redução de MM como critério para definir sarcopenia 28,8% (95% IC: 24 – 34,1%), em comparação aos estudos que combinaram força e a MM 13,2% (95 % IC: 5,2 – 22,9%). Além disso, os autores verificaram que as PVHIV têm OR 2.4 (95% IC: 1,1 – 5,3) mais chances de pertencer ao grupo sarcopenia comparativamente as pessoas vivendo sem o vírus. Inserindo na metanálise apenas os estudos que pareavam a amostra

por sexo, idade, IMC e etnia, a chance de pertencer ao grupo sarcopenia foi de OR 6,1 (95% IC: 1,1 – 33,5) para as PVHIV (OLIVEIRA; BORSARI; WEBEL; ERLANDSON *et al.*, 2020).

1.1.9 Estratégias nutricionais baseadas em proteínas e aminoácidos isolados para manutenção ou aumento dos parâmetros musculares relacionados à sarcopenia

Tendo como ponto de partida as diferentes mudanças que ocorrem no tecido muscular em PVHIV, o adequado balanço proteico muscular é fundamental para atenuar o declínio, manter ou aumentar a MM em diversas situações e, neste contexto, dentre as estratégias não-farmacológicas, o consumo de proteínas é imprescindível para manter a integridade da massa muscular (LIAO; TSAUO; WU; CHENG *et al.*, 2017).

Acerca do consumo proteico diário, alguns fatores são estudados com afinco por pesquisadores da área, como a quantidade diária, a quantidade por refeição, o tipo de proteína (p. ex., origem vegetal ou animal) ingerida, o momento de ingestão e a distribuição ao longo do dia. Além disso, a presença do exercício físico de força, o balanço energético e o estado nutricional são fatores que determinam a necessidade proteica diária (MURPHY; CHURCHWARD-VENNE; MITCHELL; KOLAR *et al.*, 2015; OIKAWA; MCGLORY; D'SOUZA; MORGAN *et al.*, 2018; STOKES; HECTOR; MORTON; MCGLORY *et al.*, 2018).

Portanto, tendo em vista que todos estes elementos influenciam o efeito das proteínas alimentares sobre os parâmetros relacionados à MM, discussões pautadas na necessidade proteica diária foram feitas na última década. Acerca da quantidade proteica diária para manutenção da MM, apesar de pequenas variações, a recomendação para adultos (19 – 65 anos de idade), independente do sexo e sedentários, é de 0,8 – 0,9 g/kg/dia segundo a *Recomended Dieary Allowance* (RDA), Organização Mundial da Saúde (OMS) e *European Food Safety Authority* (EFSA) (JOINT, 2007; RICHTER; BAERLOCHER; BAUER; ELMADFA *et al.*, 2019; TRUMBO; SCHLICKER; YATES; POOS *et al.*, 2002), ao passo que para idosos, estes valores alcançam 1,0 – 1,2 g/kg/dia (DEUTZ; BAUER; BARAZZONI; BIOLO *et al.*, 2014; NUNES; COLENSO-SEMPLE; MCKELLAR; YAU *et al.*, 2022; RICHTER; BAERLOCHER; BAUER; ELMADFA *et al.*, 2019). Considerando que a necessidade proteica sofre influência do estado nutricional, para idosos em desnutrição ou risco de desnutrição por conta de doenças agudas ou crônicas, esses valores podem alcançar 1,2 – 1,5 g/kg/dia (BAUER;

BIOLO; CEDERHOLM; CESARI *et al.*, 2013; DEUTZ; BAUER; BARAZZONI; BIOLO *et al.*, 2014).

Em idosos, o aumento da necessidade proteica se deve, principalmente, à resistência anabólica. Esse fenômeno muscular está vinculado à menor disponibilidade de aminoácidos pós prandiais, menor fluxo sanguíneo ao tecido muscular, resistência à insulina e à menor capacidade de captação de aminoácidos pelo tecido muscular; ainda, nesse cenário, menores concentrações de aminoácidos intramusculares limita a ativação de proteínas envolvidas na SPM (MOORE; CHURCHWARD-VENNE; WITARD; BREEN *et al.*, 2015; MORTON; TRAYLOR; WEIJS; PHILLIPS, 2018; ROBINSON; BURD; BREEN; RERECICH *et al.*, 2013).

Para aumentar a MM sugere-se quantidades de proteína ≥ 1,6 g/kg/dia (NUNES; COLENSO-SEMPLE; MCKELLAR; YAU *et al.*, 2022). Contudo, os dados disponíveis são divergentes conforme o método de avaliação da composição corporal, implicando em interpretações limitadas. Os estudos que avaliaram a massa magra ou massa livre de gordura não conseguem ter exatidão na quantidade MM que aumenta em resposta à ingestão proteica. Este dado é relevante e explica, parcialmente, o motivo pelo qual os resultados de função muscular serem heterogêneos entre os estudos, uma vez que os incrementos em outros componentes da massa magra e massa livre de gordura provavelmente não impactarão na força muscular (CERMAK; RES; DE GROOT; SARIS *et al.*, 2012; MORTON; MURPHY; MCKELLAR; SCHOENFELD *et al.*, 2018; WIRTH; HILLESHEIM; BRENNAN, 2020). Por exemplo, os resultados de estudos que avaliaram o efeito da suplementação proteica sobre a força de preensão manual ou testes de função (p. ex., velocidade de marcha) são amplamente variados (NUNES; COLENSO-SEMPLE; MCKELLAR; YAU *et al.*, 2022).

Levando em consideração a dificuldade de alcançar a quantidade proteica diária necessária, especialmente por alterações gastrintestinais frequentes nas PVHIV, suplementos proteicos, de aminoácidos isolados ou de compostos nitrogenados poderiam promover efeitos positivos sobre os parâmetros associados à sarcopenia. Nesse contexto, embora alguns aminoácidos isolados (p. ex., leucina), combinação de aminoácidos (p. ex., aminoácidos de cadeia ramificada) ou compostos nitrogenados (p. ex., creatina monohidratada) sejam utilizados para aumentar os parâmetros relacionados à MM, os resultados entre os estudos são divergentes. Vale reforçar que muito destes estudos observaram respostas musculares agudas, como a SPM, que não corresponde necessariamente a hipertrofia muscular esquelética (MITCHELL; CHURCHWARD-VENNE; PARISE; BELLAMY *et al.*, 2014).

Por exemplo, a leucina, apesar de ser o principal aminoácido responsável por estimular a SPM, isoladamente, seus efeitos sobre a massa e a força muscular são heterogêneos (MARTINEZ-ARNAU; FONFRIA-VIVAS; CAULI, 2019). De maneira similar, os estudos que avaliaram os parâmetros relacionados à sarcopenia após a suplementação de aminoácidos de cadeira ramificada identificaram resultados variados e, ainda, os autores sugerem cautela na interpretação, devido a baixa qualidade metodológica dos estudos (ISMAIEL; BUCSA; FARCAS; LEUCUTA *et al.*, 2022). Os componentes da sarcopenia também foram associados à ingestão diária de aminoácidos de cadeia ramificada por meio da alimentação e não foram observadas associações significativas (EBRAHIMI-MOUSAVI; HASHEMI; BAGHERI; HESHMAT *et al.*, 2022). Os estudos que avaliaram o efeito da suplementação de creatina sobre os parâmetros relacionados à sarcopenia também encontraram respostas variadas em homens e mulheres idosas (DEVRIES; PHILLIPS, 2014; DOS SANTOS; DE ARAUJO; CANDOW; FORBES *et al.*, 2021). Recentemente, Choi *et al*. (2021) verificaram o efeito de diversas intervenções nutricionais sobre os parâmetros relacionados à sarcopenia em idosos. Apenas a suplementação de creatina, com base em 4 estudos, promoveu aumento da MM, enquanto os parâmetros: FPP, força de extensão de joelho, teste de levantar da cadeira e o teste de levantar-se e ir, não modificaram perante a suplementação de creatina (CHOI; KIM; BAE, 2021). Fato é que os parâmetros relacionados à sarcopenia (p. ex., massa muscular, força muscular e desempenho físico) respondem de maneira heterogênea entre os estudos.

Em PVHIV os resultados são ainda mais escassos e variados. Poucos estudos avaliaram o efeito da suplementação proteica, de aminoácidos isolados ou de compostos nitrogenados sobre os parâmetros relacionados à sarcopenia em PVHIV. Grande parte dos estudos avaliou, apenas, a MM e os resultados observados são frágeis e limitados em função da baixa qualidade metodológica dos estudos (AGIN; GALLAGHER; WANG; HEYMSFIELD *et al.*, 2001; SAKKAS; MULLIGAN; DASILVA; DOYLE *et al.*, 2009; SATTLER; RAJICIC; MULLIGAN; YARASHESKI *et al.*, 2008).

É esperado, porém, que a necessidade proteica de PVHIV seja maior, similar a de idosos, tendo em vista as alterações musculoesqueléticas apresentadas e o ambiente inflamatório observado nesta população. Entretanto, ao menos por ora, os estudos disponíveis são insuficientes para determinar qualquer tipo de recomendação proteica ou de suplementos específicos para parâmetros relacionados à sarcopenia em PVHIV.

2 JUSTIFICATIVA

Perante os efeitos do HIV e da terapia antirretroviral, pessoas que vivem com HIV enfrentam, em razão das diversas alterações morfológicas, imunológicas e metabólicas, um persistente quadro de imunoativação e inflamação sistêmica de baixo grau que promove múltiplas mudanças capazes de culminar em desordens musculoesqueléticas, como a sarcopenia. Isso posto, compreender e identificar os aspectos relacionados à sarcopenia e os seus fatores associados em pessoas vivendo com HIV permitirá o manejo antecipado dessa condição, sobretudo por intervenções não-farmacológicas, possibilitando melhor prognóstico e qualidade de vida dessa população.

3 HIPÓTESES

Diante das implicações do HIV e das terapias antirretrovirais no organismo, hipotetizamos:

1. Que a prevalência de estar sob risco de sarcopenia seja maior entre as pessoas vivendo com HIV comparativamente às não infectadas, bem como a qualidade de vida relacionada à sarcopenia de pessoas vivendo com HIV seja menor comparativamente às pessoas que não vivem com HIV;
2. Que a força muscular e a massa muscular, bem como o desempenho físico de pessoas vivendo com HIV sejam menores comparativamente às pessoas que não vivem com HIV;
3. Que a prevalência de sarcopenia, dinapenia e obesidade dinapênica seja maior entre as pessoas vivendo com HIV comparativamente às pessoas que não vivem com HIV;
4. Que as terapias antirretrovirais com inibidores de protease estejam associadas à menor força e massa muscular de pessoas vivendo com HIV;
5. Que a utilização prévia de antirretrovirais de antiga geração, como zidovudina, estavudina, indinavir e ritonavir, esteja associada à menor força muscular e massa muscular de pessoas vivendo com HIV;
6. Que a utilização prévia de antirretrovirais de antiga geração, como zidovudina, estavudina, indinavir e ritonavir, esteja associada à maior quantidade de gordura corporal de pessoas vivendo com HIV;
7. Que o tempo da doença e o tempo de utilização da terapia antirretroviral estejam associados à menor força muscular e massa muscular de pessoas vivendo com HIV.

4 OBJETIVOS

4.1 Objetivo geral:

Compreender e identificar os fatores associados à sarcopenia em adultos vivendo com e sem HIV.

4.2 Objetivos específicos:

(i) Compreender os mecanismos relacionados às alterações musculares entre as pessoas vivendo com HIV e verificar na literatura científica os estudos que avaliaram a prevalência de sarcopenia, bem como os critérios que foram utilizados para definição de sarcopenia;

(ii) Aplicar uma ferramenta de rastreio de sarcopenia em adultos vivendo com e sem HIV;

(iii) Verificar e comparar a qualidade de vida relacionada à sarcopenia entre as pessoas adultas vivendo com e sem HIV;

(iv) Comparar os componentes da sarcopenia (p. ex., força muscular, massa muscular apendicular e velocidade de marcha) entre os adultos vivendo com e sem HIV;

(v) Verificar e comparar a frequência de dinapenia (redução da força muscular) de acordo com diferentes critérios propostos na literatura científica entre os adultos vivendo com e sem HIV;

(vi) Verificar e comparar a frequência de obesidade dinapênica (redução da força muscular associada a maior quantidade de gordura corporal) de acordo com diferentes critérios propostos na literatura científica entre os adultos vivendo com e sem HIV;

(vii) Verificar e comparar parâmetros relacionados ao estado muscular (p. ex., razão da força muscular: massa muscular e a massa muscular apendicular corrigida pelo índice de gordura corporal) entre adultos vivendo com e sem HIV;

(viii) Verificar a associação entre os diferentes esquemas de antirretrovirais utilizados atualmente e os parâmetros relacionados ao músculo esquelético (p. ex., força muscular e massa muscular) em pessoas vivendo com HIV;

(ix) Verificar a associação entre os antirretrovirais de antiga geração (p. ex., zidovudina, estavudina, indinavir e ritonavir) e os parâmetros relacionados ao

músculo esquelético (p. ex., força muscular e massa muscular) e à gordura corporal (p. ex., índice de gordura corporal e razão gordura central: apendicular) em pessoas vivendo com HIV;

(x) Verificar a associação entre o tempo de infecção pelo HIV e de uso dos antirretrovirais com os parâmetros relacionados ao músculo esquelético (p. ex., força e massa muscular) e à gordura corporal (p. ex., índice de gordura corporal e relação gordura central e massa muscular) em pessoas vivendo com HIV;

(xi) Revisar na literatura sistematicamente o efeito de potenciais intervenções nutricionais envolvendo compostos nitrogenados, sobre os parâmetros relacionados à sarcopenia em pessoas vivendo com HIV.

5 MÉTODOS

Esta tese de doutorado será apresentada em formato de coletânea de estudos científicos conforme as diretrizes da Universidade de São Paulo para apresentação de dissertações e teses. Esta tese faz parte de um estudo maior intitulado: "Dieta, inflamação sistêmica e desfechos à saúde em pessoas que vivem com HIV em terapia antirretroviral: rastreio inicial para planejamento de um estudo clínico" (Nº COEP: 3.100.321) fomentado pela Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP) (2018/25368-4- Projeto Regular).

Quatro estudos científicos compõem a presente tese e, por isso, a seção de métodos será categorizada de acordo com os artigos escritos com base nos objetivos e métodos propostos.

(i) *Sarcopenia in Persons Living with HIV under Antiretroviral Therapy: A Literature Review.*

(ii) *Sarcopenia risk, sarcopenia-related quality of life, and associated factors in people living with human immunodeficiency virus (HIV): a web-based survey.*

(iii) *Sarcopenia in people living with HIV and associated factors: a cross-sectional study.*

(iv) *Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in people living with HIV (PLWH): a systematic review*.

5.1 Estudo 1 - Persons Living with HIV under Antiretroviral Therapy: A Literature Review

Trata-se de um artigo de revisão de literatura, de natureza narrativa, com elementos de uma revisão de escopo, cujos objetivos foram (i) compreender os mecanismos relacionados às alterações musculares entre as pessoas vivendo com HIV e (ii) verificar na literatura científica os estudos que avaliaram a prevalência de sarcopenia, bem como os critérios que foram utilizados para definição de sarcopenia.

Para responder o primeiro objetivo foi conduzida uma busca na literatura científica de maneira não sistematizada nas bases de dados (p. ex., MEDLINE, Web of Science, Scopus etc.). A busca foi conduzida utilizando aleatoriamente descritores e palavras-chave relacionados ao tema como, por exemplo: "*lean body mass*", "*fat-free mass*", "*sarcopenia*", "*antiretroviral therapy*", e "*HIV*". Com intuito de ampliar a compreensão dos mecanismos fisiológicos, bioquímicos e moleculares, estudos *In vitro, In vivo* e com humanos (transversais, longitudinais

ou intervencionais) que investigaram os efeitos do HIV e das TARVs sobre parâmetros associados ao tecido muscular foram considerados e inseridos.

Para responder ao segundo objetivo, uma busca nas bases de dados foi conduzida de maneira sistematizada de acordo com o acrônimo PI(E)COS (**P** = população; **I(E)** = intervenção ou exposição; **C** = controle; **O** = desfecho; **S** = tipo de estudo). A nossa estrutura de busca considerou (**P** = adultos e idosos; **E** = HIV; **O** = sarcopenia, massa ou força muscular). A busca foi feita utilizando os termos *Medical Subject Headings* (MeSH): “Adult”, “Aged”, “HIV”, “Sarcopenia”, “Muscle Strength”, e “Muscle” e operadores booleanos "OR" e "AND". O script final para condução da busca está descrito a seguir: ((((Adult) OR (Adults)) OR (Aged)) AND ((HIV) OR (Human Immunodeficiency Virus))) AND ((((((Sarcopenia) OR (Muscle Strength)) OR (muscle)) OR (muscles)) OR (Muscle Tissue)) OR (Muscle Tissues)).

5.2 Estudo 2 - Sarcopenia risk, sarcopenia-related quality of life, and associated factors in people living with human immunodeficiency virus (HIV): a web-based survey

Objetivos

Neste inquérito, foram estabelecidos dois objetivos. O primeiro objetivo foi identificar a prevalência de estar sob risco de sarcopenia e a qualidade de vida relacionada à sarcopenia entre as pessoas que vivem com e sem HIV. Em seguida, o nosso objetivo foi verificar os fatores associados à condição de estar sob risco de sarcopenia, bem como os fatores associados à menor qualidade de vida relacionada à sarcopenia.

Tipo de estudo e características da amostra

Este estudo foi elaborado em decorrência da pandemia da COVID-19, que impactou diretamente na dinâmica de coleta de dados do nosso estudo original. Por isso, este estudo adicional foi proposto, com a inserção de ferramentas de análise que possibilitassem rastrear, mesmo que subjetivamente, parâmetros relacionados à sarcopenia, a qualidade de vida associada à sarcopenia, bem como os potenciais fatores associados ao risco de sarcopenia e qualidade de vida associada à sarcopenia em pessoas vivendo com e sem HIV.

Foi realizada uma pesquisa descritiva, exploratória e transversal online. A amostra foi não probabilística e de conveniência, e incluiu PVHIV e pessoas sem HIV (PNVHIV), como grupo de comparação. As PVHIV pesquisadas eram pacientes cadastrados em uma clínica

chamada de Serviço de Extensão aos Pacientes (SEAP), da Divisão de Moléstias Infecciosas do Hospital das Clínicas da Universidade de São Paulo, SP, Brasil. Os participantes foram convidados por um aplicativo online de mensagens a partir dos contatos obtidos no serviço.

As PNVHIV foram convidadas pelas mídias sociais, usando o método "*snowball sampling*" ou bola de neve; logo, trata-se de uma amostra não probabilística. Para serem incluídos, os participantes poderiam ser de qualquer sexo, ter 18 anos ou mais, residir no estado de São Paulo. Além disso, não poderiam apresentar hepatite C, doença renal crônica ou câncer. O Comitê de Ética da Universidade de São Paulo aprovou o presente estudo (número: 4.938.460) **(ANEXO A)**, e todos os participantes assinaram o Termo de Consentimento Livre e Esclarecido. Os dados foram coletados entre agosto e dezembro de 2021, exclusivamente online por uma plataforma de coleta de dados chamada SurveyMonkey®.

Questionário

As questões foram selecionadas a partir de discussões entre os pesquisadores considerando os principais fatores predisponentes para a sarcopenia. Assim, a construção do questionário foi baseada em critérios de plausibilidade biológica e dados da literatura prévia. Portanto, tendo como base o papel da inflamação sistêmica no tecido muscular, acreditamos que as pessoas que vivem com HIV são mais suscetíveis a estarem em risco de sarcopenia e apresentarem pior qualidade de vida relacionada à sarcopenia. Ademais, pessoas que vivem com HIV enfrentam um cenário sociocultural mais complexo, expondo-as a fatores (p. ex., estigma) que podem maximizar o risco de sarcopenia e à pior qualidade de vida relacionada à sarcopenia. O questionário criado para o inquérito online foi estruturado com base em variáveis que impactam os desfechos de interesse.

A pesquisa foi composta por 112 perguntas para avaliação (i) da condição de risco de sarcopenia, (ii) da qualidade de vida relacionada à sarcopenia; (iii) da prática de exercícios físicos, (iv) do comportamento sedentário, (v) dos problemas relacionados ao sono, (vi) da presença de doenças crônicas não transmissíveis, (vii) da idade, massa corporal, estatura, perda 3 kg nos últimos meses, apetite, sexo, bebidas e hábitos de fumar; (viii) da renda e da escolaridade. Assim, inserimos no questionário principalmente fatores relacionados à sarcopenia **(APÊNDICE A)**. Além dos critérios biológicos, consideramos critérios estatísticos para verificar o grau de associação das variáveis independentes aos desfechos analisados. A seguir, a descrição das variáveis coletadas será dividida em desfechos, variáveis independentes e covariáveis.

Desfechos

Rastreio do Risco de sarcopenia

Identificamos o risco de sarcopenia com a escala SARC-F, ferramenta desenvolvida por Malmstrom e Morley (2013) e validada por Malmstrom *et al*. (2016) que reflete as alterações do estado de saúde associadas às consequências da sarcopenia **(ANEXO B)**. Seus componentes de avaliação são (i) força; (ii) auxílio para caminhada; (iii) levantar-se da cadeira; (iv) subir escadas; (v) quedas. Cada questão pontua de "zero" a "dois", obtendo, portanto, pontuação máxima de 10. Escores ≥ 4 são indicativos de risco de sarcopenia. A força muscular foi estimada pela quanta dificuldade eles tinham para levantar ou carregar 5 kg. A assistência para caminhada foi avaliada perguntando aos participantes quanta dificuldade eles tinham para atravessar uma sala e se eles usavam algum dispositivo ou precisavam de ajuda. A capacidade de levantar-se de uma cadeira avaliada perguntando aos entrevistados quanta dificuldade eles apresentavam para se levantarem de uma cadeira ou cama e se eles precisavam de ajuda. Subir escadas foi medido perguntando aos entrevistados quanta dificuldade eles tinham para subir um lance de escadas de 10 degraus. As respostas e seus possíveis escores são 0 = nenhuma dificuldade, 1 = alguma dificuldade e 2 = muita dificuldade, uso de auxílios ou incapaz de fazer sem ajuda). Finalmente, as quedas foram pontuadas com 2, 1 ou 0, respectivamente, para os entrevistados que relataram cair quatro ou mais vezes, 1-3 vezes, ou aqueles que não relataram quedas no último ano.

Qualidade de Vida Relacionada à Sarcopenia

Os questionários genéricos de qualidade de vida não são capazes de identificar diferenças entre indivíduos sarcopênicos e não sarcopênicos porque um número limitado de perguntas será relevante para a sarcopenia. Assim, o SarQoL® foi utilizado, uma vez que este questionário foi desenvolvido e validado por Beuadart *et al*. (2015) com o proposito de identificar aspectos que envolvem a qualidade de vida que provenientes da sarcopenia. O SarQoL® é um questionário de fácil aplicação que pode ser autoaplicável **(ANEXO C)**. O questionário está disponível em vários idiomas no site www.sarqol.org, e a pontuação geral da qualidade de vida foi calculada com um banco de dados Access desenvolvido para esse fim.

O SarQoL® é composto por 55 itens em 22 questões, cada uma graduada em escalas do tipo Likert de quatro pontos (frequentemente, às vezes, raramente, nunca) e intensidade (muito,

moderadamente, um pouco e nada), abrangendo as sete principais dimensões associadas à sarcopenia: (i) saúde física e mental, (ii) locomoção, (iii) composição corporal, (iv) função do músculo esquelético, (v) atividades de vida diária, (vi) atividades de lazer e (vii) medo. A pontuação total do SarQoL® varia de zero (pior condição) a 100 (melhor condição). No estudo de validação dessa ferramenta, todos os domínios individuais foram positivamente correlacionados com o escore total; entretanto, locomoção, funcionalidade e atividades de vida diária apresentaram os maiores coeficientes de correlação.

Variáveis independentes

Exercício físico e comportamento sedentário

Os participantes responderam sobre o tipo e a duração dos exercícios físicos, que foram estratificados em atividades predominantemente de longa duração (p.ex., caminhada [exceto para o trabalho] ou corrida, ciclismo, natação, *spinning*, *step*, salto, esportes coletivos como futsal/futebol, vôlei, basquete e handebol, luta, aula de dança etc.) e exercícios de força (p.ex., musculação, CrossFit®, exercício funcional, pilates ou calistenia). Os participantes poderiam responder que realizavam exercícios físicos de longa duração, força, ambos, ou não praticavam nenhum tipo de exercício físico.

O comportamento sedentário foi avaliado por meio das seguintes questões: (i) quantas horas você passa sentado assistindo televisão por dia durante a semana e nos finais de semana e (ii) quantas horas você passa sentado em seu videogame, celular, tablet, computador ou outros dispositivos por dia durante a semana e dias de fim de semana. Foram somados os valores informados (em horas) para cada questão nos dias de semana e finais de semana.

Qualidade do sono

Para avaliar os problemas relacionados ao sono, foi aplicado o Mini-Sleep Questionnaire (MSQ), desenvolvido por Zoomer *et al.* (1985), traduzido e adaptado para o português por Falavigna *et al.* (2011) **(ANEXO D)**. O MSQ contém dez itens e estima a qualidade do sono e a sonolência diurna. O MSQ é composto pelas seguintes questões: (i) Você tem dificuldade para adormecer à noite?; (ii) Você acorda de madrugada e não consegue dormir de novo?; (iii) Você toma soníferos ou tranquilizantes?; (iv) Você dorme durante o dia?; (v) Ao acordar pela manhã, você ainda se sente cansado?; (vi) Você ronca à noite (que você saiba)?;

(vii) Você acorda durante a noite?; (viii) Você acorda com dor de cabeça?; (ix) Você se sente cansado sem motivo aparente?; (x) Você tem sono agitado? (mudanças constantes na posição ou movimentos das pernas e braços). As respostas estão em uma escala *Likert* com sete pontos, com as opções de resposta: (1) nunca, (2) muito raramente, (3) raramente, (4) às vezes, (5) frequentemente, (6) muito frequentemente, (7) sempre. A pontuação do questionário varia de 0 a 60 pontos, sendo possível classificar o padrão de sono em muito bom (0-9 pontos), bom sono (10-24 pontos), sono pouco alterado (25-27 pontos), sono moderadamente modificado (28 – 30 pontos) e muito alterado (acima de 30 pontos).

Massa corporal, estatura, IMC, doenças e outras questões relacionadas à saúde

Os participantes descreveram a sua massa corporal e estatura atuais (utilizadas para calcular o IMC). Foi questionado sobre a perda de peso "você perdeu mais de 3 kg sem querer nos últimos meses?" e sobre o apetite, "você tem sentido perda de apetite?" Ainda, o questionário continha perguntas sobre a presença de doenças crônicas diagnosticadas por um médico (p. ex., diabetes mellitus (DM) tipo 1 e 2, hipertensão arterial sistêmica (HAS) ou dislipidemia). Acerca do histórico de etilismo e tabagismo, primeiramente questionamos se consumiam bebidas alcoólicas com as possíveis opções de resposta: (i) nunca bebo; (ii) menos de 1x/mês; (iii) 1x ou mais/mês; e segundo, questionou-se sobre o hábito de fumar, cujas opções de resposta foram: (i) não fumo atualmente; (ii) sim, menos que diariamente; (iii) sim, diariamente.

Covariáveis

Características sociodemográficas

Perguntamos sobre a idade (em anos), sexo ao nascer (feminino ou masculino) e escolaridade (curso primário, ensino médio, faculdade, pós-graduação [mestrado ou doutorado] ou nunca estudou). De acordo com os salários-mínimos do Brasil, também perguntamos sobre a renda mensal: < 1 salário-mínimo; 1 a 2 salários-mínimos; 2 a 3 salários-mínimos; 3 a 4 salários-mínimos; 5 a 9 salários-mínimos; 10 ou mais.

Análise estatística

O teste Shapiro-Wilk investigou a normalidade dos dados. Os dados contínuos e com distribuição normal foram apresentados de acordo com a média e o desvio padrão, enquanto os dados contínuos e não paramétricos foram apresentados de acordo com a mediana, valores mínimos e máximos.

Os dados categóricos foram apresentados de acordo com a frequência absoluta e relativa. Os grupos (PVHIV e PNVHIV) foram comparados de acordo com o tipo de distribuição utilizando o teste t de Student independente ou o teste Mann-Whitney para dados paramétricos contínuos e não paramétricos, respectivamente. Para variáveis categóricas, adotamos o teste do qui-quadrado.

Para investigar as associações entre cada variável e os desfechos de interesse (SARC-F e SarQoL®) foram utilizadas análises de regressão logística. Logo, os modelos de regressão logística foram estruturados, considerando a natureza dicotómica do SARC-F e atribuindo uma característica dicotómica à pontuação proveniente do SarQoL® (abaixo e acima da mediana).

Portanto, para os modelos de regressão logística, o SARC-F foi tratado como uma variável dicotómica, pessoas que apresentaram pontuação igual ou maior que 4 foram consideradas “em risco de sarcopenia”. Além disso, a pior qualidade de vida relacionada com a sarcopenia foi definida como inferior à mediana.

Os modelos foram construídos em três etapas, como se segue.

Primeiro passo: conduzimos os modelos simples de regressão tomando cada variável independente, sendo: viver com HIV, DM, HAS, níveis elevados de colesterol (todos sim vs. não), perda recente de peso e apetite (ambos sim vs. não), IMC (obesidade e excesso de peso vs. eutrofia), prática de exercício (sim vs. não), comportamento sedentário pelo tempo em frente à TV, tablet e outros dispositivos (contínuo), problemas relacionados com o sono (boa qualidade de sono vs. má qualidade de sono).

Segundo passo: Para serem incluídas nos modelos múltiplos, as variáveis testadas nos modelos simples devem corresponder aos seguintes critérios: (i) valor de $p < 0,20$; (ii) ausência de multicolinearidade analisada pelo fator de inflação de variância (VIF) e tolerância. Consideramos uma variável estatisticamente significativa quando o valor de p foi $\leq 0,05$.

Terceiro passo: Nos modelos múltiplos criados, idade (contínua), sexo (masculino vs. feminino), nível de escolaridade (até à escola secundária vs. faculdade ou mais), e o rendimento

mensal (até 2 salários-mínimos brasileiros vs. mais) foram inseridos como variáveis de ajuste. Nos modelos ajustados as variáveis foram consideradas estatisticamente significativas quando o valor p era ≤ 0,05. Todos os testes estatísticos foram realizados com JAMOVI® versão 2.2.5 Versão sólida para macOS.

Com intuito de obter informações acerca do tamanho amostral e evitar associações estatísticas equivocadas ou extrapolações indevidas, o cálculo do tamanho amostral *a posteriori* foi conduzido tendo como base nos seguintes critérios (i) proporções observadas para pessoas em risco de sarcopenia com base no SARC-F apenas entre as pessoas vivendo com HIV e proporção observada de pessoas consideradas com menor escore global do SarQoL® para amostra completa; (ii) tamanho da amostra e (iii) número de variáveis independentes inseridas no modelo múltiplo. O cálculo do tamanho amostral foi feito por meio do G*Power versão 3.1.9.6.

5.3 Estudo 3 - Sarcopenia in people living with HIV and associated factors: a cross-sectional study.

Objetivos

(i) Verificar e comparar a frequência de sarcopenia e dinapenia (redução da força muscular) de acordo com os diferentes constructos propostos na literatura científica em pessoas adultas vivendo com e sem HIV;

(ii) Verificar e comparar os componentes da sarcopenia (p. ex., força muscular, massa muscular apendicular e velocidade de marcha) em pessoas adultas vivendo com e sem HIV;

(iii) Verificar e comparar a frequência de obesidade dinapênica (redução da força muscular associada a maior quantidade de gordura corporal) de acordo com os diferentes constructos propostos na literatura científica em pessoas adultas vivendo com e sem HIV;

(iv) Verificar e comparar os parâmetros relacionados ao estado muscular (p. ex., razão da força muscular: massa muscular e a massa muscular apendicular corrigida pelo índice de gordura corporal) entre pessoas adultas vivendo com e sem HIV;

(v) Verificar a associação entre os componentes da composição corporal, hábitos de vida e outros parâmetros de saúde com a força e a massa muscular de pessoas vivendo com e sem HIV;

(vi) Verificar a associação entre os diferentes esquemas de antirretrovirais utilizados atualmente e os parâmetros relacionados ao músculo esquelético (p. ex., força muscular e massa muscular) em pessoas adultas vivendo com e sem HIV;

(vii) Verificar a associação entre os antirretrovirais de antiga geração (p. ex., zidovudina, estavudina, indinavir e ritonavir) e os parâmetros relacionados ao músculo esquelético (p. ex., força muscular e massa muscular) e à gordura corporal (p. ex., índice de gordura corporal e razão gordura central: apendicular) em pessoas adultas vivendo com e sem HIV;

(viii) Verificar a associação entre o tempo de infecção pelo HIV e de uso dos antirretrovirais e os parâmetros relacionados ao músculo esquelético (p. ex., força muscular e massa muscular) e à gordura corporal (p. ex., índice de gordura corporal e razão gordura central: apendicular) em pessoas adultas vivendo com e sem HIV.

Tipo de estudo, recrutamento e características da amostra

Trata-se de uma pesquisa transversal, descritiva e exploratória com amostra não probabilística, composta por dois grupos de participantes: pessoas vivendo com HIV (PVHIV) e pessoas sem o vírus (PNVHIV). Previamente ao desenvolvimento deste estudo, foi realizada uma pesquisa online (estudo submetido à publicação) com PVHIV e PNVHIV e, a partir deste estudo anterior, foram recrutadas as que manifestaram interesse em participar deste novo estudo. Com intuito de reduzir vieses e diferenças entre os grupos, o recrutamento de cada PNVHIV foi pareado com um PVHIV de acordo com o sexo e a idade.

Os critérios para inclusão no estudo, para ambos os grupos, foram: idade igual ou superior a 18 anos, de qualquer sexo, residentes no estado de São Paulo e livres de Hepatite C, doença renal crônica ou câncer. Ainda assim, as PVHIV precisavam ter carga viral indetectável (< 50 cópias/mL) e estar sob qualquer terapia antirretroviral. Os dados foram coletados entre agosto de 2021 e maio de 2022.

Procedimentos éticos

O Comitê de Ética da Universidade de São Paulo, SP, Brasil aprovou o estudo (protocolo número: 3.100.321), e todos os participantes assinaram o termo de consentimento **(ANEXO E)**.

Desfechos (variáveis dependentes)

Avaliação da força muscular

A força muscular foi avaliada por meio do dinamômetro que mensura a força de preensão manual Jamar® (FPM). Este dinamômetro possui um indicador estático de fácil leitura, com escala de 0 – 90 kg e resolução de 2 kg. A força de preensão foi medida em ambas as mãos na posição sentada com o braço em um ângulo de 90 graus, de acordo com as diretrizes do National Health and Nutrition Examination Survey (NHANES) para dinamometria de mão. A força de preensão palmar foi medida três vezes, com intervalo de 1 minuto entre as medidas, e a pontuação mais alta foi usada para cada mão (ROBERTS; DENISON; MARTIN; PATEL *et al.*, 2011).

Avaliação da composição corporal

A avaliação da composição corporal foi feita pela absorciometria de raios-X de dupla energia (DEXA) (Lunar iDXA, GE Healthcare, com plataforma de software enCORE). A DEXA é relativamente barata, com rápida capacidade de varredura e exposição à radiação. Os voluntários foram colocados em decúbito dorsal na maca do equipamento com os braços em pronação e os pés em dorsiflexão. Uma fonte de raios X acima do voluntário emitiu fótons em dois níveis distintos de energia específicos para tecidos moles e osso cortical. Um colimador fica situado entre o paciente e a fonte de raios X para mitigar a emissão. As atenuações dessas emissões de fótons de baixa e alta energia foram detectadas e combinadas para criar uma imagem planar para avaliar a composição corporal.

Os participantes foram orientados a chegar ao laboratório pela manhã, em jejum, sem realizar exercícios físicos extenuantes no dia anterior e com roupas leves, sem metais. Os dados utilizados neste estudo incluíram massa gorda total (MG; kg e %), massa magra total (MM; kg), MG e MM dos braços e pernas. Ainda, a massa magra apendicular (MMA; soma da MM dos braços e pernas), massa gorda apendicular (MGA; soma da MG dos braços e pernas) foram calculadas. Em seguida, foi calculado o índice de MM apendicular (IMMA) a partir da MMA

dividida pela altura ao quadrado (MMA/e^2) e o índice da MG (IMG) foi obtido a partir da MG dividida pela altura ao quadrado (BAZZOCCHI; PONTI; ALBISINNI; BATTISTA *et al.*, 2016).

Avaliação do desempenho físico

A velocidade da marcha foi avaliada para determinar a severidade da sarcopenia àqueles que cumprirem os critérios anteriores. Esta variável foi obtida em segundos, a partir de três tentativas consecutivas, percorrendo a distância de 4,6 m. Os valores médios foram considerados. Foram colocadas quatro marcações de fácil visualização no piso, totalizando 8,6 m. Consideramos a distância entre a primeira e a segunda marca (2 m) como a fase de aceleração e a distância entre a terceira e a quarta marca (2 m) como a fase de desaceleração. O tempo entre as marcações 2 e 3 (4,6 m) foi obtido por meio de um cronômetro. Orientamos os participantes a realizarem sua velocidade habitual de caminhada. A velocidade da marcha foi medida em segundos (s) e metros por segundo (m/s) (ABELLAN VAN KAN; ROLLAND; ANDRIEU; BAUER *et al.*, 2009).

Definições relacionadas à sarcopenia e dinapenia

Os parâmetros relacionados à sarcopenia (força muscular e IMMA) foram tratados de três maneiras, sendo (i) contínuas para comparar PVHIV e PNVHIV, (ii) considerando o ponto de corte do *Working Group on Sarcopenia in Older People* (EWGSOP) para menor força e massa muscular (FPM: < 27 kg para homens e < 16 kg para mulheres e IMMA: < 7,0 kg/m^2 para homens e < 5,5 kg/m^2 para mulheres) (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019), e (iii) de acordo com o ponto de corte do *Sarcopenia Definitions and Outcomes Consortium* (SDOC) para menor força e massa muscular (FPM: < 35,5 kg para homens e < 20 kg para mulheres e IMMA: < 7,26 kg/m^2 para homens e < 5,45 kg/m^2 para mulheres) (BHASIN; TRAVISON; MANINI; PATEL *et al.*, 2020). Indivíduos que apresentaram menor força muscular pela FPM segundo os pontos de corte do EWGSOP ou SDOC foram definidos como dinapenia. A combinação de menor FPM e menor IMMA de acordo com os pontos de corte do EWGSOP ou SDOC foi utilizada para definição de sarcopenia. Para determinar o grau de severidade da sarcopenia o desempenho físico pelo teste de velocidade de marcha foi considerado. Àquele cujo tempo dispendido foi < 0,8 m/s, além dos outros critérios descritos acima, foi classificado como sarcopenia severa.

Obesidade dinapênica e obesidade abdominal dinapênica

Para definir obesidade dinapênica, consideramos a menor FPM de acordo com os critérios EWGSOP e SDOC associada ao IMC > 30 km/m^2. Para definir obesidade central dinapênica, consideramos menor FPM associada a circunferência da cintura > 102 cm para homens e > 88 cm para mulheres (DE OLIVEIRA MAXIMO; DE OLIVEIRA; RAMIREZ; LUIZ *et al.*, 2021).

Variáveis independentes

Parâmetros relacionados à composição corporal

Convertemos o IMMA e IMG em z-score de acordo com o valor de referência do *National Health and Nutrition Examination Survey* (NHANES) provenientes da publicação de KELLY; WILSON e HEYMSFIELD (2009). Os z-scores foram calculados pela seguinte equação: $Z = (score - mean)/SD$.

Em seguida, utilizamos o IMMA e o IMG para calcular o IMMA ajustado para o IMG ($IMMA_{IMG}$), conforme os passos a seguir.

Primeira etapa: Foi determinado o escore Z do IMMA previsto em relação ao escore Z do IMG usando regressões apropriadas para idade, sexo e etnia provenientes do estudo de WEBER; LONG; LEONARD; ZEMEL *et al.* (2016) , sendo:

Escore Z previsto do IMMA = β1 (escore Z do IMG) + β2 (escore Z do IMG)^2 + constante

Segunda etapa: foi gerado o escore Z do $IMMA_{IMG}$ individual incorporando o escore Z do IMMA da etapa 1 acima e o desvio padrão apropriado para sexo e etnia usando a seguinte equação (WEBER; LONG; LEONARD; ZEMEL *et al.*, 2016):

$IMMA_{IMG}$ = (escore Z do IMMA atual – escore Z do IMMA previsto * (1/SD))

A classificação de baixa $IMMA_{IMG}$ foi definida quando o escore Z fosse ≤ -1,0 desvio padrão (WEBER; LONG; LEONARD; ZEMEL *et al.*, 2016).

Qualidade muscular

A partir da força muscular pela FPM, foi determinado o índice de qualidade muscular (MQI). Este índice consiste na FPM dividida pela MMA. Contudo, o equipamento DEXA utilizado para este estudo não oferece os valores de massa magra dos braços separadamente. Assim, escolhemos o MQI_{total}, que foi definido como a FPM (valores da mão dominante + não dominante) dividido pelo IMMA (LORENA CRISTINA CURADO LOPES, 2022).

Antropometria, doenças e outras questões relacionadas à saúde

Todos os participantes foram avaliados em jejum de no mínimo 4 horas, com roupas leves, e sem sapatos com base nas recomendações do NHANES (FRYAR; CARROLL; GU; AFFUL *et al.*, 2021). As avaliações foram feitas três vezes de maneira consecutiva e os valores médios foram usados para todos os cálculos.

A massa corporal foi aferida por meio de uma balança digital com precisão de escala de 100 g. A estatura foi medida por meio de um estadiômetro portátil com precisão de 0,1 cm. Os sujeitos foram instruídos a ficarem próximos ao estadiômetro, com a cabeça na posição de Frankfurt. A medição foi feita ao final de uma inspiração profunda. Todas as circunferências foram medidas com fita inelástica. Os participantes foram instruídos a ficar em pé com os braços cruzados sobre os ombros contralaterais e a fita foi colocada no ponto médio entre a espinha ilíaca ântero-superior e abaixo da última costela para avaliar a circunferência da cintura. Em seguida, a fita foi fixada na circunferência máxima da musculatura glútea para avaliar a circunferência do quadril. A circunferência da panturrilha foi medida com os indivíduos sentados com a perna em um ângulo de 90 graus. A fita foi fixada na circunferência máxima no plano perpendicular à linha longitudinal da panturrilha. Um pesquisador experiente mediu todas as circunferências.

O índice de massa corporal (IMC) foi obtido dividindo-se o peso pela estatura ao quadrado e a classificação aplicada foi < 18,5 kg/m^2 para baixo peso, 18,5 a 24,9 kg/m^2 para peso normal, 25,0 a 29,9 kg/m^2 para sobrepeso e > 30,0 kg/m^2 à obesidade, segundo a OMS (WEIR; JAN, 2022). Ainda, a razão cintura-quadril foi calculada dividindo-se a circunferência da cintura pela circunferência do quadril.

Em relação às doenças e outras questões relacionadas à saúde, os participantes foram questionados sobre a presença de doenças crônicas diagnosticadas por um médico [diabetes mellitus (DM tipo 1 e 2), hipertensão arterial sistêmica (HAS), dislipidemia ou doença

gastrointestinal]. Os hábitos de consumo de álcool foram respondidos como (i) nunca bebo; (ii) 1x ou mais/mês. O hábito de fumar foi respondido como (i) não fumo atualmente; (ii) sim, fumo diariamente, semanalmente ou mensalmente.

Variáveis de ajuste

Características sociodemográficas

Consideramos como variáveis de ajuste para os modelos de regressão: idade (em anos), sexo ao nascer (feminino ou masculino), escolaridade (curso fundamental, ensino médio, faculdade, pós-graduação [mestrado ou doutorado] ou nunca estudou) e etnia (branca e não branca) foram referidos pelos participantes. De acordo com o salário-mínimo brasileiro, perguntamos sobre a renda mensal: < 1 salário-mínimo; 1 a 2 salários-mínimos; 2 a 3 salários-mínimos; 3 a 4 salários-mínimos; 5 a 9 salários-mínimos; 10 ou mais.

Análise estatística

Pelo teste de Shapiro-Wilk investigamos a normalidade dos dados. Os dados contínuos com distribuição normal foram apresentados de acordo com a média e o desvio padrão, enquanto os dados contínuos e não paramétricos foram apresentados de acordo com a mediana, e os valores mínimos e máximos. Os dados categóricos foram apresentados como valores absolutos e relativos. Os grupos (PVHIV e PNVHIV) foram comparados pelo teste t de Student Independente ou teste de Mann-Whitney, de acordo com o tipo de distribuição. Para variáveis categóricas, adotou-se o teste Qui-quadrado.

Para investigar as associações entre cada variável dependente e os desfechos (FPM e IMMA), conduzimos modelos de regressão linear, considerando a distribuição gaussiana de ambas. Para força muscular consideramos os valores provenientes da FPM e para a massa muscular os valores provenientes do DEXA, que foram utilizados para calcular o IMMA a partir da MMA.

Calculamos a MMA com base na publicação de Heymsfield *et al.* (1990) (HEYMSFIELD; SMITH; AULET; BENSEN *et al.*, 1990). Assim, a MMA é derivada da massa total dos braços e das pernas menos a quantidade de gordura e massa óssea desses membros. A MMA é o parâmetro relacionado ao músculo esquelético mais utilizado para verificar as alterações da massa muscular e os fatores associados em estudos de sarcopenia

(YAMADA; YAMADA; YOSHIDA; MIYACHI *et al.*, 2021). Embora estudos anteriores com as PVHIV tenham usado o consenso EWGSOP (GHAYOMZADEH; HACKETT; SEYEDALINAGHI; GHOLAMI *et al.*, 2022), outros estudos usaram a definição do SDOC (ERLANDSON; TRAVISON; ZHU; MAGAZINER *et al.*, 2020), e a maioria dos estudos definiu sarcopenia pelo baixo IMMA (< 2 DP) (BAUMGARTNER; KOEHLER; GALLAGHER; ROMERO *et al.*, 1998; GALLAGHER; VISSER; DE MEERSMAN; SEPULVEDA *et al.*, 1997). Além disso, no modelo de regressão para verificar os fatores associados ao IMMA, não foram inseridas as variáveis relacionadas ao músculo esquelético (p. ex., massa magra, massa magra dos braços e pernas ou MMA) tendo em vista a alta multicolinearidade.

Os modelos foram construídos em três etapas, conforme segue:

Inicialmente fizemos os modelos univariados. Estes modelos simples foram feitos considerando FPM e o IMMA como variáveis dependentes.

Para a FPM testamos como variáveis independentes: viver com HIV, os parâmetros relacionados à adiposidade corporal (p. ex., MG total, MG de braços e pernas, MGA, IMG, relação gordura do tronco e apendicular, relação MG e MM) e relacionada à massa muscular (MM, MM dos braços e das pernas, MMA, IMMA e a velocidade de marcha), bem como idade e sexo.

Para o IMMA testamos como variáveis independentes: viver com HIV, os parâmetros relacionados à adiposidade corporal (p. ex., MG total, MG de braços e pernas, MGA, IMG, relação gordura do tronco e apendicular, relação MG e MM) e os parâmetros relacionados à função muscular (p. ex., FPM e velocidade da marcha), bem como idade e sexo.

Segunda etapa: modelos múltiplos. Para serem incluídas no modelo múltiplo 1, as variáveis testadas nos modelos univariados deveriam atender às seguintes condições: (i) ter relevância biológica com base no pressuposto teórico relacionado à sarcopenia; (ii) valor de $p \leq 0,20$; (iii) após o atendimento destas condições, a construção dos modelos múltiplos foi feita observando a ausência de multicolinearidade analisada pelo fator de inflação de variância (VIF) e pela tolerância (KIM, 2019). Por esse motivo, verificamos a multicolinearidade, principalmente, quando variáveis relacionadas à gordura corporal e relacionadas ao músculo esquelético foram inseridas nos modelos múltiplos. Neste caso, para escolher apenas uma variável independente relacionada à gordura corporal e à massa muscular para inserir nos

modelos múltiplos, consideramos o valor do beta mais alto e o menor *Akaike Information Criterion* (AIC) (CHAURASIA; HAREL, 2012).

Etapa três: ajuste por variáveis confundidoras: como variáveis de ajuste para FPM e IMMA: tabagismo (não-fumante foi a referência), ingestão de álcool (não beber foi a referência), escolaridade (educação básica foi a referência), renda (< 1 a 3 salários-mínimos foi a referência). Ademais, as variáveis que diferiram na análise de comparação entre grupos foram inseridas para evitar vieses nas associações.

Ainda, modelos de regressão foram feitos apenas com as PVHIV, incluindo as variáveis que foram significativas no modelo múltiplo ajustado e as informações relacionadas as TARVs, como tempo de doença, duração do tratamento, nadir do $CD4^+$, esquema de TARV atual [INTR associado a INI (referência); INNTR associados a INTR; ou qualquer medicamento associado aos IP e o tempo da TARV atual. Finalmente, o uso das drogas antigas relacionadas ao músculo esquelético foram testadas, como zidovudina, estavudina e ritonavir. A variável foi considerada significativa nos modelos múltiplos quando o valor de p foi $\leq 0{,}05$. Todas as análises estatísticas foram realizadas com o JAMOVI® versão 2.2.5 *Solid Version* para macOS.

Com intuito de obter informações acerca do tamanho amostral e evitar associações estatísticas equivocadas ou extrapolações indevidas, o cálculo do tamanho amostral *a posteriori* foi conduzido tendo como base nos seguintes critérios (i) o tamanho de efeito das variáveis dependentes (p. ex., FPM e IMMA) calculado pelo critério de Glass's *delta* aplicado em condições em que o desvio padrão dos grupos é diferente e, assim, usando apenas o desvio padrão do grupo controle; (ii) a partir do tamanho de efeito, verificamos o poder da amostra (beta) de acordo com o número das variáveis independentes inseridas nos modelos múltiplos da regressão linear criados para a FPM e para o IMMA. O cálculo do tamanho amostral foi feito por meio do G***Power* versão 3.1.9.6.

5.4 Estudo 4 - Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in persons living with HIV (PLWH): a systematic review

Tipo de estudo

Trata-se de uma revisão sistemática da literatura seguindo as recomendações do *The Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) e recomendações metodológicas da *Cochrane Collaboration*. O protocolo do estudo foi registrado no PROSPERO (CRD42019139981).

Pergunta de revisão

A questão de pesquisa foi baseada na formulação PICOS da seguinte forma: **População:** pessoas vivendo com HIV (PVHIV); **Intervenção:** intervenções dietéticas utilizando qualquer tipo de compostos nitrogenados (aminoácidos, proteínas, creatina ou outros); **Controle:** qualquer tipo de grupo controle, ou sem grupo controle; **Desfecho:** massa muscular esquelética; **Tipo de estudo:** estudos clínicos intervencionistas, paralelos ou cruzados, duplo cegos, cegos ou abertos, randomizados ou não randomizados. Assim, nossa pergunta de pesquisa foi formulada como: "*As intervenções nutricionais com proteínas, aminoácidos ou outros compostos nitrogenados são capazes de melhorar a massa muscular esquelética em PVHIV?"*.

Estratégias de pesquisa

As bases de dados pesquisadas foram MEDLINE/PubMed, EMBASE, LILACS, SCOPUS e Web of Science. Além disso, pesquisamos literatura cinzenta consultando as ferramentas do Google. No PUBMED, buscamos descritores indicados pelo MeSH e operadores booleanos "OR" e "AND", como segue: ((((((HIV)) OR (Human Immunodeficiency Virus)) OR (Immunodeficiency Virus, Human)) OR (Human Immunodeficiency Virus)) OR (Human Immunodeficiency Virus)) OR (Acquired Immunodeficiency Syndrome Virus)) AND ((((((((((((Nutritional Therapy)))) OR (Therapy, Nutrition))) OR (Medical Nutritional Therapy)) OR (Medical Nutritional Therapy)) OR (Therapy, Nutrition Medical)) OR (Food Supplements)) OR (Food Supplement)) OR (Food Supplements)) OR (Food Supplements)) OR (Diet Supplements)) OR (Food Supplements)) OR (Food Supplements)) OR (Food Supplement)) OR (nutraceuticals)) OR (diet, food and nutrition))) AND (((((((((Body

Composition) OR (Body Composition)) OR (Composition, Body)) OR (Composition, Body)) OR (Muscle)) OR (Muscle)) OR (Muscle Tissue)) OR (Muscle Tissue)) OR (Lean Body Mass)) OR (Fat Free Mass)) OR (Lean Mass)).

Ainda, a partir da ferramenta Google®, identificamos sites da área (HIV, composição corporal), utilizando as mesmas palavras-chave. A última busca foi realizada em 24 de agosto de 2020, sem qualquer restrição da data anterior.

Critérios de elegibilidade

Para serem incluídos, os estudos deveriam ser clínicos de intervenção, sem restrição de sexo ou estado nutricional. Foram incluídos apenas estudos em adultos. As publicações deveriam incluir a maioria dos participantes sob uso de TARV. As intervenções deveriam ser com suplementos nutricionais como proteínas íntegras, aminoácidos ou outros compostos nitrogenados (p. ex., creatina), com qualquer duração de intervenção, maneira de administração e dose, com ou sem grupo controle. A massa muscular esquelética poderia ser avaliada por qualquer método validado, duplamente indireto ou indireto (p. ex., antropometria, bioimpedância elétrica, absorciometria de raios X de dupla energia, ressonância magnética, tomografia computadorizada, pletismografia por deslocamento de ar, pesagem hidrostática ou marcadores bioquímicos). Os idiomas de publicação deveriam ser inglês, espanhol ou português. Os critérios de exclusão foram: (i) quanto ao desenho do estudo: estudos com modelos não humanos ou *In vitro* ou revisões de literatura; (ii) em relação aos participantes: gestantes, pessoas que descreveram presença de AIDS no momento do experimento (categoria "C", ou III ou IV segundo a OMS), participantes com co-morbidades diferentes do HIV que fossem associadas à perda muscular; (iii) quanto à intervenção: uso de esteroides anabolizantes, inibidores da miostatina, hormônio do crescimento; ou estudos utilizando qualquer outra terapia alternativa para o HIV diferente da TARV.

Procedimentos para desenvolver a revisão sistemática

Nossa revisão sistemática foi desenvolvida de acordo com as seguintes etapas:

1º passo. Leitura dos títulos e resumos, excluindo os não relacionados à questão de pesquisa e as duplicatas. Essa etapa foi realizada de forma independente por dois autores (MVLSQ e CMM) e verificada pelo terceiro autor (SMLR); inconsistências foram resolvidas em uma reunião de consenso.

2º passo. Obtenção dos artigos selecionados na íntegra e leitura para identificação detalhada dos critérios de inclusão e exclusão. Dois autores realizaram esta etapa de forma independente (MVLSQ e CMM), e as divergências foram resolvidas em reunião de consenso com o terceiro autor (SMLR).

3º passo. Extração dos dados dos estudos pelo primeiro autor (MVLSQ), conferidos pelo segundo autor (CMM) e organizados em arquivo Excel 2013. Os dados extraídos foram: local e duração do estudo, objetivos do estudo, desenho do estudo, características da amostra, esquema de terapia antirretroviral, tipo de intervenção, grupo controle (se houver), tempo de intervenção, informações sobre atividade física e controle da dieta, informações sobre efeitos colaterais da intervenção, métodos de análise da composição corporal, principais resultados e síntese dos achados.

Avaliação de qualidade (risco de viés)

O risco de viés foi avaliado independentemente por dois pesquisadores (MVLSQ e CMM), usando a ferramenta Cochrane de risco de viés v.2 e usando o software RoB2; divergências foram novamente resolvidas a partir de uma reunião de consenso incluindo o terceiro autor (SMLR). A crítica dos resultados foi feita com base no cegamento, na randomização dos grupos, alocação, método utilizado para avaliar a composição corporal, presença de conflitos de interesse, diferenças entre os grupos em parâmetros relevantes pré-intervenção e taxa de desistência.

6 RESULTADOS

Os resultados desta tese serão apresentados considerando a ordem dos artigos descrita acima e os objetivos propostos. Os artigos publicados ou em revisão (1, 2 e 4) foram anexados na íntegra, em formato PDF, conforme publicação ou submissão. O **Artigo 3**, que será avaliado pela comissão julgadora, foi inserido integralmente em documento de word.

O **Artigo 1** foi intitulado *Sarcopenia in Persons Living with HIV under Antiretroviral Therapy: A Literature Review* foi publicado na revista *AIDS Reviews* (*AIDS Reviews*, 2022-03-01, vol.24 (1), p.1-15) fator de impacto 2,5.

O **Artigo 2** foi intitulado *Sarcopenia risk, sarcopenia-related quality of life, and associated factors in people living with human immunodeficiency virus (HIV): a web-based survey.* Este está submetido na revista *AIDS* (Fator de impacto 4.177).

O **Artigo 3** com os dados da coleta presencial, que será avaliado pela banca, não foi submetido para nenhuma revista científica, conforme descrito pelas diretrizes da Universidade de São Paulo para apresentação de dissertações e teses. Logo, este artigo, só poderá ser submetido após a defesa de tese. Seu título provisório é *Sarcopenia in people living with HIV and associated factors: a cross-sectional study.*

O **Artigo 4** foi intitulado *Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in people living with HIV (PLWH): a systematic review*. Este artigo foi submetido na revista *Clinical Nutrition* ESPEN. Artigo aceito para publicação no dia 07/07/2022.

6.1 Artigo 1 – Sarcopenia in Persons Living with HIV under Antiretroviral Therapy: A Literature Review

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Sarcopenia in persons living with HIV under antiretroviral therapy: Literature review

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Abstract

The epidemiological profile of people living with HIV (PLWH) has expressively changed since the introduction of antiretroviral therapy (ART), from a high mortality rate to a profile similar to those living with chronic diseases. Despite the advances and effectiveness of ART, there are still various challenges to overcome, and we highlight the increased risk of sarcopenia in PLWH. This review study aims to (i) explore the pathophysiological background of sarcopenia in PLWH under the different existing ART and (ii) develop a mini-systematic review searching epidemiological studies investigating sarcopenia prevalence in PLWH. As our main findings: we established the risk of sarcopenia development, under a sequential path involving HIV, ART, immune activation, low-grade systemic inflammation, metabolic disorders, and changes in protein synthesis and breakdown in skeletal muscle tissue; some ART drugs, mainly reverse transcriptase inhibitors and protease inhibitors, contribute to critical metabolic changes, lowering the autophagy, increasing mitochondrial dysfunction and insulin resistance, which favor the development of inflammation and muscle protein breakdown. There is still insufficient data to discuss the effects of the new generation drugs, namely integrase inhibitors and fusion inhibitors, on skeletal muscle. More studies are needed to better clarify these relationships.

Keywords

HIV. Skeletal muscle. Sarcopenia. Skeletal muscle. Low-grade systemic inflammation. Antiretroviral therapy.

Introduction

Throughout the last decades, the development and improvements of HIV antiretroviral therapies (ART) enormously changed the epidemiological course of the persons living with HIV (PLWH) by lowering the viral load and consequently reducing AIDS-related mortality[1]. However, despite the important benefits of ARTs, many side effects of these drugs have been observed, contributing to the development of non-AIDS-related chronic diseases. Several physiological responses to ART can explain these effects, particularly a chronic immune activation with a consequent low-grade systemic inflammation (LGSI)[2]. One of the relevant outcomes of this is the increased risk of developing muscle disorders such as sarcopenia.

Sarcopenia is a progressive and generalized skeletal muscle disorder, now recognized as a disease (ICD-10-CM - M62.84)[3]. Its definition changed throughout the years, from emphasizing the reduced muscle mass to poor muscle strength and low muscle mass. This disease is generally associated with aging (primary sarcopenia), but its development can begin earlier in

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life due to many contributing causes beyond aging (secondary sarcopenia); it increases the likelihood of adverse outcomes such as physical frailty, disabilities, and mortality[3].

Many authors have identified a high prevalence of sarcopenia, or low muscle mass, in PLWH[4], reinforcing the importance of understanding this issue. Despite this, studies discussing the different ART-related effects on muscle are still scarce. This manuscript aims to explore the pathophysiological background of sarcopenia in PLWH and the association with the current ARTs. To achieve this aim, we divided the study into two parts: (i) a narrative review of physiological mechanisms to understand the relationship between HIV, ART, and sarcopenia (ii) a mini-systematic review searching epidemiological studies investigating sarcopenia in PLWH. Considering that the definition of sarcopenia changed very recently, we will include in this review, besides studies with the new definition, studies with the oldest ones, most of them focusing only on muscle mass.

Part 1. Physiological relationship between HIV, ART, and skeletal muscle disorders

Skeletal muscle is the body's most abundant tissue and is involved in several functions. Skeletal muscle is a primary target for glucose and lipid uptake, plays a vital role in immunoregulation, and is determinant for physical performance; these factors are associated with functionality, cardiorespiratory capacity, quality of life, and longevity[5]. It has been demonstrated that greater muscle mass at midlife is associated with successful aging in men[6].

The body muscle mass decreases approximately 1-2% per year after 50 years old in HIV-uninfected people. The nadir of muscle mass occurs at about the age of 80 years old[5]. Notably, the loss of muscle strength, so-called dynapenia, occurs between 2 and 5 times faster than muscle mass loss[5]. Both muscle mass and strength losses have been associated with several metabolic disorders and raise the odds of diseases, incapacities, and mortality[5]. Several factors are associated with muscle changes, such as physical exercise (type, intensity, and frequency), dietary and sleep patterns, illnesses, licit and illicit drugs, and neuronal disorders[5]. Imbalances in skeletal muscle turnover, namely, blunted muscle protein synthesis and increased protein breakdown, are reported in aging and pathological conditions[7].

Moreover, the motor unit (a primary functional component of the neuromuscular system for generating strength and movement) and satellite cells decrease with aging. The myosin heavy chain isoform IIa, shortening of sarcomere length, and high fat infiltration in muscle tissue appear to be contributors or parallel factors to muscle atrophy[5]. Interestingly, muscle-related changes especially occur in type II fibers, mainly responsible for muscle strength[5].

Aging, systemic inflammation, and skeletal muscle: similarities between normal aging and HIV infection

Aging is characterized by an LGSI status, a process named *inflammaging*[8]; it is part of the immunosenescence and includes organs with immunometabolic activity, such as adipose tissue and gut[8]. In turn, PLWH presents a persistent residual HIV infection, together with the ART effects, responsible for a persistent immune activation and, consequently, an LGSI. Some authors named this process "InflammAIDS[8]," and a hypothesis of anticipated aging in PLWH has been commonly accepted. Below, we will describe some features of inflammaging and the correspondent aspects of HIV infection.

Aged (senescent) cells

An essential characteristic of aging, both chronological and pathological, is cell senescence. Among various features, senescent cells reduce the capacity of dealing with antigenic molecules, metabolites, apoptotic cells, and other so-called danger-associated molecular patterns (DAMPs). In response to these patterns, the cells activate the inflammasomes[8]. Inflammasomes are multiprotein complexes capable of activating intracellular pathways and consequently nuclear factors (such as the nuclear factor kappa-beta [NF-κB]), increasing the expression and secretion of inflammatory cytokines (for instance, interleukin [IL]-6, IL-8, and Il-1α and tumor necrosis factor [TNF-α])[8]. Notably, the increase in TNF-α gene expression interacts negatively with proteins related to muscle protein synthesis (protein kinase B)[8]. In addition, NF-κB activates a proteasome-dependent pathway for protein degradation (through binding to a molecule represented by MuRF1)[9]. This process is accompanied by reactive oxygen species production that increases the muscle protein breakdown. Furthermore, the inflammasome activation reduces the expression of genes involved in autophagy, constituting, therefore, a vicious cycle which, among other consequences, fuels oxidative stress, and muscle protein breakdown[8].

Comparatively, PLWH presents a reduction in autophagy and impairs cellular removal of debris (DAMPs). Furthermore, the persistence of HIV in some cells can constitute a so-called pathogen-associated molecular pattern (PAMP); thus, DAMPs and PAMPs in PLWH's cells lead to a senescent phenotype[10].

Increased body fat

Another concept included in inflammaging is an increase and redistribution of body fat. The high-fat content of adipose tissue leads to the recruitment of M1-type macrophages[11], changing the adipocytokines secretion; there is a decrease of the anti-inflammatory molecules (i.e., adiponectin and IL-10) and an increase in the pro-inflammatory ones (i.e., IL-1β, IL-6, TNF-α, C-reactive protein [CRP], and among others)[11].

In PLWH, some ART drugs, such as protease inhibitors (PIs) and reverse transcriptase inhibitors, and some of the newest generation drugs (integrase inhibitors [IIs]) increase the body fat content[12]. The increased body fat leads to the LGSI, enhancing the risk of developing insulin resistance and diabetes, increasing the risk of reducing muscle strength and quality[13]. Therefore, fat accumulation in PLWH creates an inflammatory environment similar to the aging process[12].

Leaky gut

The aging process changes the bacterial profile of gut microbiota and enhances the immune activation, changing tolerance of gut-associated lymphoid tissue (GALT). These changes weaken the gut epithelium's barrier function, which increases intestinal permeability, allowing the passage of bacterial fragments to the bloodstream[14]. The most studied bacterial fragment from the intestine is lipopolysaccharide (LPS), from Gram-negative bacteria's outer membrane[14]. Similarly, in PLWH, the primary HIV infection and replication occur in GALT, leading the intestinal epithelial cells to be compromised, increasing gut permeability with consequent LPS translocation. Although the ART drugs improve gut immune activation, they cannot return to basal (pre-infection) levels[14].

Once in the circulation, LPS binds to specific pattern-recognizing receptors in different body tissues. Skeletal muscle has both receptors for LPS and cytokines (i.e., toll-like receptor-4 and TNF-a receptor, respectively); the signaling pathway of these receptors activates protein kinases, which can phosphorylate the insulin receptor substrate-1 (IRS-1), decreasing insulin signal transduction, impairing, among many metabolic pathways, the protein synthesis[15]. Furthermore, activation of both receptors can trigger the inflammatory cascade mediated by the NF-κB, leading to the above-described responses. Furthermore, metabolic endotoxemia provoked by LPS is associated with high body fat, glucose intolerance, raised pro-inflammatory mediators, and macrophages' infiltration in adipose tissue, constituting, therefore, a vicious cycle[14].

We can put together, at this point, immune activation, gut permeability, increased adiposity, insulin resistance, reduced protein synthesis, and increased protein degradation. In skeletal muscle cells, these interrelated processes are explanations for the reduced quantity and quality of muscle mass, or sarcopenia. Recently, Natsag et al. (2017)[16] verified, in a multicenter cross-sectional study, that PLWH presented low muscle density, accompanied by a high fat infiltration; these changes were related to insulin resistance and low activity of enzymes involved in lipid metabolism[13]. Therefore, ectopic fat accumulation in muscle can be a crucial factor for muscle-related disorders, mainly due to the increased inflammatory process[13].

Immune activation, inflammatory environment, and skeletal muscle in PLWH

Erlandson et al. (2013)[17] showed in PLWH that low $CD4^+/CD8^+$ T-cells ratio, the high CD38/HLA-DR expression on $CD8^+$ T-cells, and the high IL-6 levels were associated with increased odds of low functional status (odds ratio [OR], ≥ 1.1 for all analyses). The same authors found that reduced levels of IGF-1 (OR 5.0; 95% confidence interval [CI]: 1.4-20.0) and IGF-1 binding protein-3 (OR 3.3; 95% CI: 1.7-9.9) were associated with low functional capacity, and both were associated with increased inflammatory status[18]. In contrast, other authors verified that although inflammatory mediators (i.e., soluble CD14, CRP, and IL-6) and immunosenescent phenotype (by $CD57^+$) were high in PLWH than HIV-uninfected subjects, none of these biomarkers were associated with physical performance in 21 years old (54-69 years) PLWH under ART[19].

Langkilde et al. (2015)[20] verified that IL-6 and soluble urokinase plasminogen activator receptor were significantly associated with low muscle mass index. Recently, de Almeida et al.[21] pointed out that high CRP levels were associated with sarcopenia in PLWH, reinforcing the relationship between inflammation and sarcopenia.

Inflammaging and hormones related to skeletal muscle metabolism

High blood levels of inflammatory molecules promote the reduction of the action of anabolic hormones such as IGF-1 and reduction in myoblast determination protein-1 (MyoD-1), both molecules necessary for proliferation and differentiation of satellite cells[22]. Therefore, we can infer that both aged persons without HIV and PLWH present hormonal disturbances related to compromised muscle maintenance.

The statements above clarify that muscle disorders, including sarcopenia, are shared by aging and HIV infection under ART. Discussions about muscle mass disorders in PLWH began before ART development when AIDS-associated cachexia was frequently identified. HIV infection was recognized as a wasting disease, which can directly affect the functionality, leading to a risk of physical dependency and anticipation of death[23].

Participation of the ART on some deleterious effects in skeletal muscle

At present, there are six classes of drugs used in ART, developed according to the stages of viral replication. Briefly, the nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) compete with natural deoxynucleotides for incorporation into a growing viral DNA chain, preventing viral DNA formation[24]. The non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit the reverse transcriptase after binding and form a hydrophobic pocket proximal to the active site, leading to a change in the substrate-binding site structure and reducing the polymerase activity[24]. Integrase inhibitors (IIs) act negatively on the enzyme integrase, whose function is to catalyze the viral DNA and transfer the strand from the 3' end of the final processing; they bind to the specific complex between integrase and viral DNA, blocking the viral replication process[24]. Protease inhibitors (PIs) inhibit the HIV-1 protease enzyme responsible for breaking down the gag and viral gag-pol polyprotein precursors during the maturation of the virus. The entry inhibitors are subdivided into fusion inhibitors (FIs), which binds to gp41 and disrupts membrane attachment, and chemokine Receptor-5 (CCR-5) antagonists, which block the CCR receptor on the T-Cell to prevent viral attachment[24]. It is recommended to combine different drug classes in the ART, and the more common combinations include two NRTIs and another drug that can be NNRTIs, PIs, or IIs. Furthermore, according to the individual's responsiveness to ART, it is possible to use one entry inhibitor[24].

The different ART categories are pointed to reduce the amount and function of proteins and enzymes that regulate muscle tissue's metabolism, consequently decreasing muscle functionality. These risks assume particulars importance in PLWH facing concomitant disorders related to the aging process[25]. The effects of ARTs on mitochondrial functioning are associated with muscle metabolism. For instance, The PIs, especially the early generation (i.e., indinavir and full-dose ritonavir), can inhibit essential proteins of energy metabolism and promote several negative metabolic changes, culminating in ART-associated chronic diseases. Adverse changes in the gene expression of several proteins responsible for mitochondrial biogenesis and the lower mitochondria efficiency led to increased intramuscular metabolites such as reactive oxygen species, increasing the senescent feature of the cells. Besides, excessive accumulation of intramuscular triacylglycerol can compromise oxidative efficiency and increase the inflammatory status and insulin resistance[16].

Moreover, reduced autophagy mediated by ARTs and the consequent accumulation of DAMPs triggers systemic inflammation. Likewise, ART-related effects on gut microbiota could increase leaky gut and inflammatory status. Together, these alterations are suggested to mitigate, by several pathways, muscle protein synthesis and, in parallel, increase the activity of muscle protein breakdown. Table 1 presents a summary of studies evaluating the relationship between ART's and disorders potentially associated with skeletal muscle diseases, mainly sarcopenia. Moreover, in figure 1, we summarize the mechanisms explaining sarcopenia risk in PLWH.

Part 2. Studies investigating the prevalence of sarcopenia in PLWH

In the last decade, HIV-associated sarcopenia has been described more frequently by researchers in the field. The understanding of sarcopenia-related parameters in PLWH under ART has increased in the last decade, showing that insufficient muscle mass and strength contribute to other conditions. However, the disagreements between the appropriate methods to evaluate and diagnose this disease turn it challenging to compare the different studies, both in HIV-infected and non-infected persons. This issue is highlighted by

Table 1. Studies investigating the ART's effect on indicators of sarcopenia

ART Class	Drug	Mechanism of action	Outcome	Sample	Reference
NRTI	AZT	Changes in mitochondria quality and mitochondria complex I and III activity	Negatively affect mitochondria electron transport chain	*In vitro/ in vivo*	26
		mtDNA depletion and autophagy decreases	Accumulation of dysfunctional mitochondria and increase in ROS production	*In vitro*	27
		Decreased muscle mtDNA	Reduction of oxidative efficiency	*In vivo*	28
		Blunted cytochrome oxidase activity and mtDNA	Decrease 40% of mitochondrial volume fraction	*In vivo*	29
		AZT induces mitochondrial defects primarily in muscles with the highest oxidative capacities	Decrease muscle performance during a contractile activity at 2 and 5 Hz	*In vivo*	30
		AZT affect muscle mtDNA	AZT decreases muscle mtDNA by DNA polymerase gamma in vitro	Humans	31
PI	IDV	PI negatively affect proteins involved in MPS and MBP	Indinavir decreased MPS (42%) compared with control and reduced eIF4F complex	*In vitro*	32
		Effect of PI on glucose uptake	Indinavir decreases GLUT-4 on the cell surface	*In vivo*	33
		Insulin resistance and low MPS	High glucose levels, insulinemia and HOMA, low testosterone levels, and basal MPS	*In vivo*	34
		Indinavir induces insulin resistance in HIV-noninfected subjects	Indinavir increases fasting glucose, insulin, insulin:glucose ratio and HOMA index	Humans	35
	SQV, r, IDV, nelfinavir or combinations	--	Gain in fat mass without changes in LBM	Humans	36
	LPV/r or ATV/r	Lopinavir induces insulin resistance	ATV/r reduced visceral fat, improved muscle glucose uptake and lipid profile	Humans	37
	r, ATV, LPV e DRV	Lower expression of CD-36 and CPT-1	Less oxidation of fatty acids and increased fatty acids in the blood and accumulation in the liver and muscle	Humans	38
	RAL + ATV/r or DRV/r	Atazanavir improves insulin sensitivity	DRV/r reduced muscle density	Humans	39

(Continues)

Table 1. Studies investigating the ART's effect on indicators of sarcopenia

PI + NRTI	IDV; SQV; r, and 3TC	PI and NRTI, glycemic and lipid profile, and body composition	PI, not 3TC, worsens glycemic and lipid profile regardless of body composition changes	Humans	40
PI only; PI + NRTI + PI; PI +NNRTI	Two protease inhibitors or 2 NRTI + 1 protease inhibitor, or 2 NRTIs + 1 nonnucleoside NNRTI	--	HAART was associated with LBM increases in men, without differences in women	Humans	41
PI vs. NNRT vs. PI plus NRTI	Nelfinavir; IDV; EFZ; NVP; delavirdine; AZT + 3TC; d4T + 3TC; ABC + 3TC; ABC + d4T	Verify the effect of ART on body composition after 4-month and 5-year follow-up	PI, NNRTI, or PI plus NNRTI increases FFM, without differences between groupsw	Humans	42
PI or NNRTI plus NRTI or only NNRTI	ATV/r or EFZ + TDF /FTC or ABC/3TC	Speculate increased chronic inflammatory process	Increase in LBM in the first 96 weeks ART use with consequent reduction after 96 weeks	Humans	43
NRTI, INTI, and PI	TDF/FTC plus ATV/r or DRV/r and RAL	Limited data on the effect of integrase inhibitors and NRTI has been linked with lipoatrophy, while PI has been linked with hyperlipotrophy	ATZ/r, RAL, and DRV/r increases LBM, without differences between groups	Humans	44

LATV: atazanavir; AZT: zidovudine; r: ritonavir; DRV: darunavir; TDF: tenofovir; 3TC: lamivudine; ABC: abacavir; FTC: emtricitabine; EFZ: efavirenz; IDV: indinavir; LPV: lopinavir; SQV: saquinavir; NVP: nevirapine; ROS: reactive oxygen species; mtDNA: mitochondrial DNA; eIF4F: eukaryotic initiation factor 4F; GLUT-4: glucose transporter type 4; HOMA: homeostasis model assessment; LBM: lean body mass; HAART: highly active antiretroviral therapy; FFM: fat-free mass.

the experts responsible for the last updated consensus about sarcopenia, the European Working Group on Sarcopenia in Older People (EWGSOP2)[3].

Previous studies verified that PLWH under ART presents less muscle strength[45], although others have seen no difference compared with HIV-uninfected subjects[46]. The loss of muscle strength has shown an association with several muscle-related disorders, and EWGSOP2 considers as the primary parameter to be assessed for sarcopenia diagnosis[3]. Functionality analysis is crucial since systematic reviews and meta-analyses found that in PLWH, muscle strength and aerobic capacity are lower than in non-infected controls[47].

Due to biochemical changes in muscle tissues, poor muscle strength and reduced aerobic capacity are commonly found simultaneously. In this context, Ortmeyer et al. (2016)[13] described that the activity of some enzymes responsible for energy metabolism, namely B-HAD and Citrate Synthase, and peak oxygen consumption (VO_{2peak}) was lower in PLWH compared to healthy counterparts. Moreover, lower muscle plasticity commonly observed in older adults seems to occur in PLWH, as demonstrated by Jankowski et al. (2020)[48]. The authors evaluated aged PLWH after 24 weeks of physical exercise (n = 18; ART > 2 years) and compared with HIV-uninfected subjects (n = 21); they observed that adaptations promoted by training are much more relevant in HIV-uninfected subjects[48]. Considering the lower responsiveness to exogenous stimuli promoted to maintain muscle functionality even in ART subjects, understanding these changes is essential.

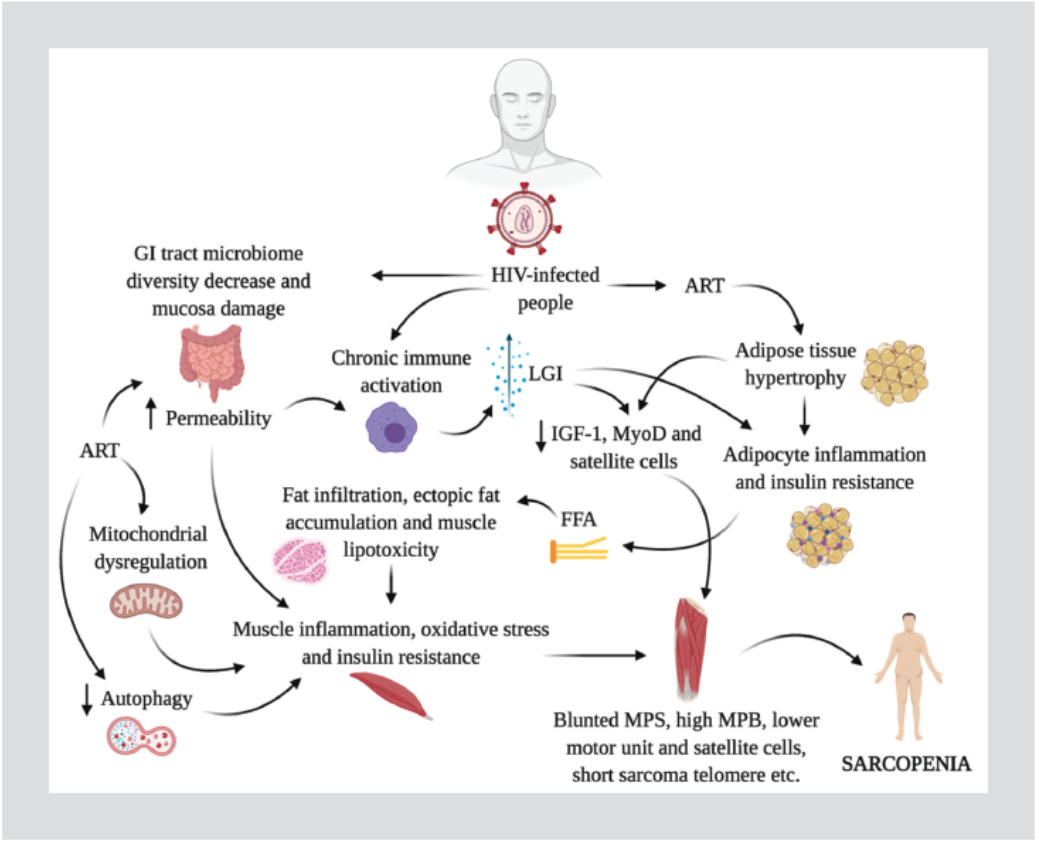

Figure 1. *Potential mechanisms of action to explain sarcopenia in PLWH.*
Created with BioRender.com. 1. HIV promotes changes in the gut microbiota shape and intestinal epithelial cells, increasing the leaky gut process. The translocation of metabolites (i.e., LPS) promotes immune activation in immune and non-immune cells, such as skeletal muscle. Inflammation in muscle tissue increases oxidative stress and insulin resistance (with bidirectional interface), which may reduce MPS. 2. Chronic immune activation increases LGSI, which can decrease the activity of substances responsible for MPS (i.e., IGF-1, MyoD, and Satellite Cells). 3. LGSI and ART modify adipose tissue functionality, which can lead to insulin resistance and increase the circulation of FFA, which act as inflammatory triggers, creating a vicious cycle. 4. Ectopic fat accumulation due to adipose tissue dysfunction can promote muscle protein turnover changes, increasing MPB. 5. ART promotes mitochondrial damage (i.e., toxicity, less efficiency, and less mitophagy) by increasing muscle tissue inflammation.

Trying to identify studies investigating the prevalence of sarcopenia in PLWH, we performed a literature search exclusively in the PubMed database, adopting MeSH terms for HIV and sarcopenia respective entry terms; the search included articles published up to January 2021, without the previous restriction of date. Sixty-two studies were found, and after analyzing the title and summary, 20 studies were selected for reading in full. After this step, we choose the studies that took sarcopenia (regardless of the diagnostic criteria) as a primary or secondary outcome, which resulted in 13 studies described in table 2. Below, we highlight the main features of these studies.

Several criteria were used to diagnose pre-sarcopenia and sarcopenia, being (i) European Working Group on Sarcopenia in Older People 1 (EWGSOP 1); (ii) European Working Group on Sarcopenia in Older People 2 (EWGSOP 2); (iii) Foundation of the National Institutes of Health Sarcopenia Project (FNIH); (iv) Sarcopenia Definitions and Outcomes Consortium (SDOC); (v) Asian Working Group for Sarcopenia (AWGS); (vi) and Baumgartner's criteria. It is important to note that numerous factors can modify the prevalence of sarcopenia. For instance, lean mass can be assessed by electrical bioimpedance (BIA) and energy X-ray absorptiometry (DXA). Muscle strength can be assessed by the grip strength or chair stand test.

Table 2. Studies investigating sarcopenia, or sarcopenia-related outcomes, in PLWH.

Author (year)	Location	Sample (n)	Age (years)	Current therapy	HIV-1 RNA and CD4	Duration of HIV infection (Years)	Sarcopenia related results	Method of sarcopenia diagnosis
Buehring et al. (2012)[49]	USA	66	41.5 (23-68)	Treatment naive PI + NNRTI NRTI	Viral load: 136.68 Nadir CD4: 233	7 (1-19)	Sarcopenia (21.9%)	Muscle strength:- LBM: DXA Muscle function:- < 2 standard deviations ALM/m^2 (< 7.26 kg/m^2) Baumgartner's criteria
Erlandson et al. (2013)[18]	USA	359	52.1 ± 0.3	When stratified by low and high-functioning subjects Low function Tenofovir (24; 80%) Protease inhibitor (n = 24; 80%) High function Tenofovir (41; 85%) Protease inhibitor (n = 32; 67%)	Current CD4+ T-cells/µL 600 (16) Detectable HIV-1 RNA (≥ 48 copies/mL) 18 (5)	Not reported	27 (35%) met the criteria for low muscle mass 15 (50%) of the low muscle function subjects were classified as sarcopenic	Muscle strength:- LBM: DXA Muscle function: SPPB and the 400-m walk Low muscle mass was defined as ASMI < 5.45 kg/m^2 for women and < 7.26 kg/m^2 for men Baumgartner's criteria
Wasserman; Segal-Maurer; Rubim (2014)[50]	USA	80	54 (50-60)	NRTI + NNRTI + INSTI or NRTI + NNRTI + PI	Indetectable viral load and CD4 cells/mm^3 > 500	15.5 (10-19)	Sarcopenia (5%) Pre-sarcopenia (20%) No sarcopenia (75%)	Muscle strength: HGD LBM: BIA Muscle function: gait speed EWGSOP 1 criteria
Neto et al. (2015)[51]	Brazil	33	59 ± 7	Lamivudine + Zidovudine (n = 17) Lamivudine + Tenofovir (n = 16) Efavirenz (n = 13)	Undetectable viral load (90.9%)	7.15 ± 3.74	Sarcopenia: HIV$^+$ = 24.2%; n = 8 Pre-sarcopenia: HIV$^+$ = 12.1%; n = 4 No sarcopenia: HIV$^+$ = 63.6%; n = 21	Muscle strength: HGD LBM: BIA Muscle function: gait speed EWGSOP 1 criteria
Dutta et al. (2017)[52]	Indian	103	35 (32-41)	n = 94 NRTI n = 88 NNRTI n = 6 PI	HIV-1 RNA < 50 c/mL not reported CD4 = 460 (365-640)	4.75 (2.1-8.1)	PSMM in controls and males with HIV was 67.08 ± 4.11% and 63.74 ± 10.66%, respectively	Muscle strength:- LBM: DXA Muscle function:- PSMM (total LM/weight x 100) < 2 SD below

(Continues)

Table 2. Studies investigating sarcopenia, or sarcopenia-related outcomes, in PLWH *(Continued)*.

Echeverría et al. (2018)[53]	Spain	860	52 (47-57)	Not reported	HIV-1 RNA < 50 c/mL (n = 94%) CD4 = 552 (377-728)	8 (3-15)	Sarcopenia in whole sample = 25.7% Female 57 % Male 27 % Sarcopenia in the age ≥ 50 years Female (n = 55; 43%) Male (n = 33; 8.8%)	Muscle strength: - LBM: DXA Muscle function: - The cut-off point used was two SD below the mean SMI Baumgartner's criteria
Hawkins et al. (2018)[54]	USA	199	60.1 (54.4-63.8)	Cumulative years on ART 12.5 (9.1–15.3) Cumulative years on TDF 5.5 (1.2–8.7) Cumulative years on PI 7.6 (1.7–13) Cumulative years on ZDV or D4T 6.9 (3.3–11.2)	HIV-1 RNA < 50 c/mL n = 179 (90%) CD4 = 641 (500-843)	Not reported	Sarcopenia HIV+ (n = 32; 17%	Muscle strength: HGD LBM: DXA Muscle function: gait speed (4-meter course Sarcopenia criteria-only ASMI
Abdul Aziz et al. (2018)[55]	Malaysia	315	43 (37-51)	Not reported	HIV-1 RNA < 50 c/mL n = 179 (90%) CD4 = 550 (394-760)	Not reported	HIV+ (n = 15; 10%)	Muscle strength: HGD LBM: BIA Muscle function: Gait speed (4-m course Sarcopenia using definitions adapted from the AWGS
Oursler et al. (2019)[56]	USA	31	62.1 ± 6.6	Tenofovir (n = 17) NNRTI (n = 10) Protease inhibitor (n = 4) ISTI (n = 20)	HIV-1 RNA < 20 c/mL (n = 27) CD4 = 683.9 (293.4)	20.4 (8.3)	n = 4 (13%) ASMI cut-off values. None of these cases of sarcopenia had low grip strength	Muscle strength: HGD LBM: DXA Muscle function: - Baumgartner's criteria and Grip strength (EWGSOP)
Debroy et al. (2019)[57]	Italy	169	56.8 ± 5.9	Not reported	HIV-1 RNA < 50 c/mL (n = 90%) CD4 = 628 (479-792)	18.9 (6.5)	n = 42 (27.8%)	Muscle strength: HGD LBM: DXA Muscle function: - Baumgartner's criteria

(Continued)

Table 2. Studies investigating sarcopenia, or sarcopenia-related outcomes, in PLWH *(Continued)*.

de Almeida et al. (2020)[21]	Brazil	83	Sarcopenia = 62.4 ± 8.1 Pre-sarcopenia = 56.4 ± 5.2 No sarcopenia 57.0 ± 6.0	Not described	HIV-1 RNA Sarcopenia = 363.6 (1046.4) Pre-sarcopenia = 35.1 (75.4) No sarcopenia = 289.5 (1542.7) CD4 cells/mm^3 Sarcopenia = 609.3 (283.7) Pre-sarcopenia = 513 (176.2) No sarcopenia = 614.8 (251.9)	Not described	Sarcopenia (n = 10) Pre-sarcopenia (n = 14) No sarcopenia (n = 59)	Muscle strength: HGD LBM: DXA Muscle function: - EWGSOP 2 Sarcopenia was defined as low ALMI) and altered muscle strength
Oliveira et al. (2020)[58]	Brazil	302	51.7 ± 9.0	NRTI + PI (n = 134; 44.4%) NRTI + NNRTI (n = 92; 30.5%) NRTI + INSTI (n = 43; 14.2%) NRTI + PI + INSTI (n = 14; 4.6%)	75% had an undetectable HIV-1 RNA (< 40 copies/mm^3) CD4 cells/mm^3 > 500 173 (57.9%)	11.2 ± 7.7	EWGSOP 1 = 4.3% EWGSOP 2 = 1.0%	Muscle strength: HGD and chair stand LBM: BIA and DXA Muscle function: Gait speed and static balance EWGSOP 1 and 2
Erlandson et al. (2020)[46]	USA	645	Men HIV$^+$ = 59 ± 5 HIV$^-$ = 60 ± 5 Women HIV$^+$ = 50 ± 5 HIV$^-$ = 49 ± 6	Not described	HIV-1 RNA < 50 copies/mL n = 179 (Men) n = 103 (Women) CD4 + T-cells < 500 cells/uL n = 48 (men) n = 62 (women)	Not described	EWGSOP 1 Men: HIV$^+$ = 12% Women: HIV$^+$ = 3% FNIH Men: HIV$^+$ = 11% Women: HIV$^+$ = 3%	Muscle strength: HGD LBM: DXA Muscle function: Gait speed (4-m course) EWGSOP 1 FNIH

HGD: handgrip dynamometry; LBM: lean body mass; AWGS: Asian Working Group for Sarcopenia; RNA: ribonucleic acid; DXA: dual-energy X-ray absorptiometry; ALMI: appendicular lean mass; NNRTI: non-nucleoside reverse-transcriptase inhibitors; PI: protease inhibitors; NRTI: nucleoside reverse-transcriptase inhibitors; INSTI: integrase inhibitors; CD4: cluster of differentiation 4; EWGSOP: European Working Group on Sarcopenia in Older People; FNIH: Foundation of the National Institutes of Health Sarcopenia Project; BIA: bioelectrical impedance analysis; ASMI: appendicular skeletal muscle mass; SDOC: Sarcopenia Definitions and Outcomes Consortium; PSMM: percentage skeletal muscle mass (total LM/weight x 100); SPPB: Short Physical Performance Battery.

Finally, physical performance can be assessed by Gait speed and Short Physical Performance Battery (SPPB). Several studies use only one parameter (i.e., lean body mass) to define sarcopenia; others added muscle strength or muscle function. Still, parameter sequence can change pre-sarcopenia and sarcopenia definitions. For example, EWGSOP1 considered lean body mass as a primary outcome, while EWGSOP2, a revised definition of sarcopenia, recommends low muscle strength as the primary outcome, making the prevalence of sarcopenia heterogeneous across studies. EWGSOP2 has resulted in a lower sarcopenia prevalence in HIV-uninfected subjects[59].

Buehring et al. (2012)[49] found in PLWH a prevalence of sarcopenia of 21%, considering only Baumgartner's criteria. Erlandson et al. (2013)[18] evaluated body composition by DXA and functionality by Short Physical Performance Battery and the 400-m walk. The authors found that using appendicular skeletal muscle index cut points, 27 (35%) of all subjects met the criteria for low muscle mass, and 15 (50%) of the low function subjects were classified as sarcopenic. Still, the authors found higher odds for lower lean mass in subjects with low function (OR 2.5; 95% CI: 1.0-6.1).

Wasserman; Segal-Maurer; Rubim (2014)[50] verified 20% (95% CI: 12.5-31.9%) and 5% (95% CI: 1.4-12.3%) of pre-sarcopenia and sarcopenia prevalence, respectively. Pre-sarcopenia was defined operationally as low skeletal muscle index only, and sarcopenia was defined operationally as low skeletal muscle index and low muscle strength or performance. Furthermore, considering EWGSOP1 criteria, other authors found 24.2% (n = 8) and 6.7% (n = 4) of sarcopenia prevalence in PLWH and HIV-uninfected subjects, respectively[51]. Thus, studies that consider only muscle mass as a criterion for defining sarcopenia found higher prevalences[52].

Echeverría et al. (2018)[53] observed that the prevalence of sarcopenia (definition based only on low appendicular muscle mass) was 25.7% (95% CI 22.8-28.7) in PLWH. The authors also showed that the higher time that lasted from the HIV diagnosis (> 5 years) increased the risk of sarcopenia (1.78; 95% CI 1.31-2.41; $p < 0.001$).

Hawkins et al. (2018)[54] defined sarcopenia as appendicular skeletal muscle index ≤ 7.26 kg/m^2 using DXA scan. In contrast, considering only Baumgartner's criteria, sarcopenia prevalence was higher in HIV-uninfected subjects (21%) versus PLWH (17%). Interestingly, when stratified by visceral adipose tissue > 130 cm^2, sarcopenia prevalence was higher in PLWH (n = 25; 14%) versus HIV-uninfected (n = 15; 8%), suggesting that high visceral adiposity with a more inflammatory status could increase sarcopenia prevalence. Similarly, Abdul Aziz et al. (2018)[55], using the AWGS as definition criteria, verified that HIV-uninfected individuals had lower muscle mass than the infected individuals 9.56 (8.46-10.64) kg/m^2 and 10.08 (8.28-11.24) kg/m^2, respectively. When stratified by < 50 years old, 7 (7%) PLWH and 7 (7%) HIV-uninfected subjects presented sarcopenia, but when stratified by 50 years or older, 8 (17%) PLWH and only 2 (4%) HIV-uninfected presented sarcopenia.

Considering Baumgartner's criteria, some studies found that 27.8% of PLWH met the definition of sarcopenia[57], while others found only 13% prevalence of sarcopenia[56]. Interestingly, EWGSOP 2 appears to reduce the prevalence of sarcopenia, being verified that 16% and 12% met the criteria for pre-sarcopenia and sarcopenia, respectively[21]. Likewise, Oliveira et al. (2020)[58], using EWGSOP1 and EWGSOP2, evaluated sarcopenia prevalence in PLWH. The prevalence of pre-sarcopenia was 9.6% and 5.6% for EWGSOP1 and EWGSOP2, respectively. Sarcopenia prevalence was 4.3% and 1% considering EWGSOP1 and EWGSOP2, respectively.

Erlandson et al. (2020)[46] found no differences in strength and gait speed between people without HIV. Applying EWGSOP1 criteria, the prevalence of sarcopenia in men and women with HIV was 12 and 3%, respectively. In HIV-uninfected subjects, the prevalence of sarcopenia in men and women was 7 and 3%, respectively. According to the FNIH criteria, the prevalence of sarcopenia in men and women with HIV was 11 and 3%, respectively. In HIV-uninfected subjects, the prevalence of sarcopenia in men and women was 8 and 1%, respectively.

A recent systematic review and meta-analysis observed 24.1% (95% CI: 17.8-31%) prevalence of sarcopenia in PLWH. The authors also found that the prevalence was higher when considering only muscle mass (28.8%; 95% CI: 24-34.1%), while studies that defined sarcopenia by reducing muscle mass and function found an average prevalence of 13.2% (95% CI: 5.2-22.9%). Finally, studies considered to be of high methodological quality have a lower average prevalence (18%; 95% CI: 5.4-33.2%) versus moderate (27.6%; 95% CI: 20.3-35.5%) and low quality (27.5%; 95% CI: 22-33.5%). From the studies that compared the prevalence of sarcopenia in people with or without HIV, it can be seen that the prevalence of sarcopenia in HIV-uninfected subjects is 11.1% (95% CI: 1.4-26.5%); therefore, PLWH has 2.4 higher odds for sarcopenia (95% CI: 1.1-5.3)[60]. Another recent systematic review and meta-analysis assessing the prevalence of

sarcopenia in PLWH verified that the frequency of sarcopenia defined by low muscle mass (Baumgartner's operational definition) alone was 30.3% (95% CI: 24.3-37.1%) and the frequency of sarcopenia defined by low muscle mass with low muscle strength (EWGSOP definition) was 4.5% (95% CI: 1.3-13.9%)[61].

In vitro *studies*

In vitro studies that evaluated the potential effects of ARTs (especially NRTIs and PIs) on muscle tissue identified mitochondrial damage[26], reduced complex I and III activity in the electron transport chain[28], impairment autophagy[27], an increase of reactive oxygen species, and blunted of muscle protein synthesis[32].

In vivo *non-human studies*

In vivo studies also evaluated ART's effect. Several metabolic alterations were verified, such as anabolic muscle resistance[29], smaller mitochondrial biogenesis[30], insulin resistance[33,34], and lower testosterone levels[29].

Figure 2 presents the potential ART's mechanisms that could affect the skeletal muscle.

Human studies

Human studies did not directly assess the relationship between ARTs and sarcopenia (considering the combined criteria); they only associated with sarcopenia-isolated parameters (i.e., lean body mass, muscle strength, or physical function). Therefore, studies are needed for more specific associations between ARTs and sarcopenia.

One of the initial studies investigating ART's effect on muscle mass was published in 1991[31]. The authors evaluated the muscle (removed by biopsy) of 9 PLWH treated with AZT for 9-18 months and 2 PLWH who did not receive the therapy. The authors pointed that PLWH treated with AZT reduced their mtDNA. First-generation ARTs, mainly NRTI (zidovudine, zalcitabine, didanosine, and stavudine), generated mitochondrial dysfunction, impairing oxidative capacity leading to clinical manifestations such as exercise intolerance, H^+ accumulation, and muscle acidosis[62].

Silva et al. (1998)[36] evaluated PIs (saquinavir, ritonavir, indinavir, nelfinavir, or combinations) effect on the lean body mass of adult subjects. The authors found an increase in fat mass without changes in lean body mass. It is believed that changes in fat mass can be attributed to insulin resistance. The same adverse effects on glucose metabolism were seen *in vitro* and *in vivo* studies using indinavir in humans[35].

Mulligan et al. (1999)[40] compared groups treated with PIs (n = 20; 16 indinavir; 2 saquinavir; 2 ritonavir), NRTIs (n = 9; lamivudine plus other NRTI), and control group (n = 12; stable ART's other than PIs or lamivudine 3TC). The intervention time was 3.4 ± 0.5 and 4.8 ± 1.2 months in PIs and 3TC, respectively. Regarding LBM, the authors observed changes of +1.1 ± 0.6, +0.1 ± 0.6, and −0.1 ± 0.5 in the PIs, 3TC, and control groups, respectively, with no statistical difference between the groups. In addition, the authors found insulin (+12.2 ± 4.9 μU/mL), triacylglycerol (+53 ± 17 mg/dL), and LDL-cholesterol (+18 ± 5 mg/dL) increases in the PIs group, with no difference in the other groups. Thus, they conclude that the use of PIs worsened the metabolic profile, regardless of changes in body composition.

Similarly, other authors have found that PLWH PI users (ritonavir, atazanavir, lopinavir, and darunavir) had lower expression of proteins responsible for lipids' metabolism, such as CD-36 and carnitine palmitoyl transferase-1, essential for skeletal muscle fatty acid oxidation. The lower efficiency in lipid oxidation has been associated with lipolysis, high free fatty acids circulation, intrahepatic, and muscular fat accumulation[38].

Moreover, obesity prevalence's increased in recent years in PLWH. Weight gain involves subcutaneous and visceral fat depot increases[63]. High adiposity is attributed, at least in part, to adverse-related ART regimens[63]. For instance, INSTI-based regimens were associated with weight gain; however, mechanisms are unclear, speculating effects on thermogenesis, appetite, energy regulation, or direct effects on adipose tissue[63]. Katlama et al. (2020)[64] verified in 165 PLWH with viral suppression that PI switch for raltegravir and etravirine increased by 12% total, trunk and limb fat mass after 96 weeks. High adiposity can lead to ectopic fat accumulation, including muscle tissue. Intramuscular fat accumulation incurs muscle-related dysfunctions (i.e., increased inflammation, insulin resistance, and mitochondrial damage). The interaction between obesity and sarcopenia is widely discussed, with several suggested mechanisms, mainly related to the effects of inflammation, insulin resistance, and lower IGF-1 levels, stimulating muscle protein degradation and reducing muscle protein synthesis[10,16].

Few studies verified the effect of ART on lean mass, being observed a positive association between the trunk and leg lean mass and ART, especially in men[41]. Shlay et al. (2007)[42] evaluated 422 antiretroviral-naive

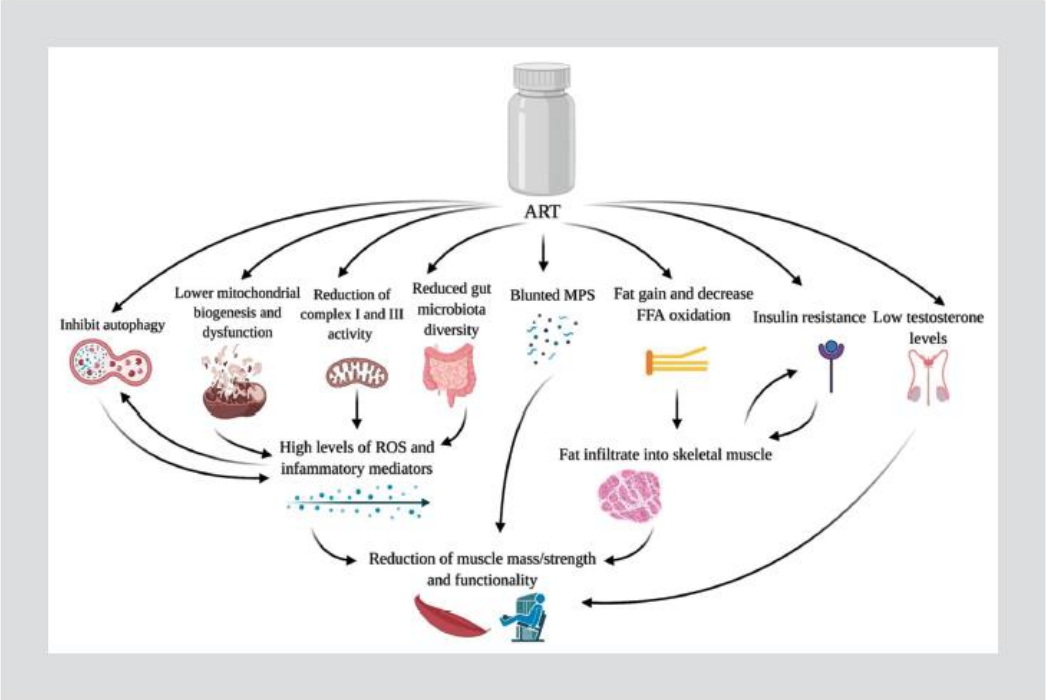

Figure 2. *Potential mechanisms of ART's drugs associated with muscle metabolism. Created with BioRender.com.*
Over the years, several ART's and combinations have been proposed to reduce viral replication and restore the immune system. It is not clear how these drugs have modified and still modify substances responsible for muscle protein turnover. 1. ART appears to reduce autophagy, increasing the accumulation of damaged molecules (DAMPs), which can maximize the inflammatory process. 2. The mitochondrial inefficiency generated by ART can contribute to the accumulation of intramuscular lipids responsible for insulin resistance and inflammation in muscle tissue. 3. ART increases the production of ROS, contributing to oxidative stress. 4. Directly, ART can reduce the gene expression of proteins involved in MPS. 5. The lower uptake and oxidation of peripheral lipids explains, at least in part, LGSI and the increase in fat infiltrate in the muscle. 6. ART, mainly protease inhibitors, are associated with insulin resistance, a crucial factor for MPB. 7. There is evidence that ART also negatively affects testosterone, an essential hormone for MPS. 8. The reduction in functionality can occur from these various changes mentioned, leading to less muscle tissue use, culminating in a muscle catabolic environment.

patients who were randomized into three groups, being: PI (n = 141; nelfinavir; indinavir; ritonavir-boosted PI); NNRTI (n = 141; efavirenz; nevirapine; delavirdine); or some PI (described above) + combination of NNRTI (n = 140; AZT +3TC; stavudine [d4T] +3TC; abacavir +3TC; abacavir + d4t). After 4 months, the authors found an increase in FFM in the PI group (1.2 kg) in the NNRTI group (1.43 kg) and the PI + NNRTI group (1.04 kg) with no statistical difference between groups. After 5 years, the authors observed an increase in FFM of 1.92, 2.02, and 1.79 kg in the PI, NNRTI, and PI + NNRTI groups, respectively, without statistical difference.

Previous studies verified metabolic parameters after switching from lopinavir/ritonavir to atazanavir/ritonavir (ATV/r). The combination of ATV/r reduced visceral fat, improved muscle glucose uptake and lipid profile[37]. These findings were confirmed more recently, ATV/r improved glucose metabolism and reduced insulin resistance, suggesting more negative effects on lopinavir use[65]. Thus, it is not possible to infer that all PIs have the same effects on body composition and metabolism.

Adrian et al. (2020)[39] found that darunavir/ritonavir (DRV/r) were associated with low lateralis muscle density (−2.43; SE =1.07; p = 0.024) and high intermuscular lateralis fat area (1.64; SE =0.80; p = 0.041). This finding suggests negative effects of DRV/r combination on muscle mass and fat mass. Still, muscle density (psoas and paraspinal) was positively associated with short physical performance physical battery (SPPB) and grip strength evaluation in men. Paraspinal muscle density was positively associated with SPPB and of women.

Therefore, it is possible to infer that the different combinations of PIs have different effects on the

muscle. While ATV/r improves glucose metabolism, DRV/r is associated with lower muscle density. This effect may be due to DRV only. Finally, raltegravir use was negatively associated with intermuscular psoas fat area. Raltegravir, an IIs, is still little explored despite the effects on body composition.

In Grant et al. (2016)[43] study, ART-naïve subjects were randomized to ATV/r or efavirenz (EFV) combined with either tenofovir/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC). During the first phase of the intervention, HIV-infected subjects increased LBM (0.53 vs. 0.06 kg/year; 95% CI for difference: 0.12, 0.82 kg/year; p = 0.008) versus non-infected subjects. In the second phase (> 96 weeks), however, HIV-infected individuals lost LBM in comparison to HIV-uninfected controls (−0.28 vs. 0.06 kg/year; 95% CI for difference: −0.51, −0.18 kg/year $P < 0.001$). These data suggest that chronically, ART appears to have negative effects on LBM. In addition, the authors found no relationship between the ART type and changes in skeletal muscle. These findings are confirmed in other studies, being verified an increase in FFM in ATZ/r (2 ± 5.8%), raltegravir (2 ± 6%), and DRV/r (1.2 ± 6.4%) groups; however, they did not observe differences in LBM between groups over 96 weeks[44].

Conclusion

Living with HIV and the aging process share similar metabolic and inflammatory changes that, by themselves, could justify the increased risk of sarcopenia in PLHW. Besides, PLWH in ART, despite the numerous benefits on the immune system and survival, have to live with the side effects of the treatment, including chronic diseases and skeletal muscle changes. However, there is still a lack of studies investigating the effects of the virus with ART on skeletal muscle metabolism. For now, it is possible to infer that living with HIV under ART is associated with persistent metabolic changes, such as lower efficiency in autophagy, insulin resistance, and mitochondrial dysfunction, increasing inflammation, and muscle protein breakdown. The inflammaging (and inflammAIDs) anticipate the aging process changes, and the adipose tissue, the gut microbiota, and some ART-drugs (NRTI, especially AZT and PIs) are involved in those processes. Concerning the new generations of drugs, mainly INIs and FIs, there is still insufficient data to assess skeletal muscle effects. More targeted studies to confirm antiretroviral drugs' effect on skeletal muscle mass, strength, and functionality, are needed to clarify the relationship between HIV, ART, and sarcopenia.

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6.2 Artigo 2 – Sarcopenia risk and sarcopenia-related quality of life, and associated factors in people living with human immunodeficiency virus (HIV): a web-based survey

Sarcopenia risk, sarcopenia-related quality of life, and associated factors in people living with human immunodeficiency virus (HIV): a web-based survey

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Abstract

Background: People living with HIV (PLWH) exhibit several metabolic disturbances and are in a chronic inflammatory state. This condition increases the odds of acquiring many disorders, including sarcopenia, a skeletal muscle disease. However, due to the difficulty of objectively assessing this disease, early identifying people at risk of sarcopenia, their quality of life, and associated factors are critical to anticipate interventions. Objectives: First, we aimed to screen for the risk of sarcopenia and sarcopenia-related quality of life in people living with and without HIV. Second, we aimed to verify associated factors to be at risk of sarcopenia and lower sarcopenia-related quality of life in PLWH. Design and Methods: this is a non-probabilistic web-based survey that included two groups of participants, one composed of PLWH and another of non-infected people (PNLWH). The participants of the PLWH group were invited directly from a university-based inpatient clinic, while PNLWH was invited from social media. Both groups responded to a web questionnaire that included the SARC-F and SarQoL® to screen people at risk of sarcopenia and their quality of life. People at risk of sarcopenia were defined by the proposed cutoff points for SARC-F (≥ 4 points), and SarQoL's overall score was categorized as follows: people who scored below the median were defined with a lower sarcopenia-related quality of life. Still, we investigated some associated factors according to biological plausibility (i. e. sedentary behavior, physical exercise practice, sleep quality, chronic diseases, smoking and drinking habits, weight, and appetite loss). We performed logistic regression models to investigate associations between each variable and outcomes (SARC-F and SarQoL®). Results: 344 participants were included [89 men (150 PLWH and 39 PNLWH) and 155 women (61 PLWH and 94 PNLWH)]. The SARC-F identified 10.43% (95 % CI: 6.6 – 15.4%) of PLWH at risk of sarcopenia; in turn, only one PNLWH was at risk of sarcopenia (0.75%; 95% CI: 1.90e-4 – 4%). SarQoL® overall scores were 76.5 (5.88 – 98.1) and 83.2 (5.88 – 100) for PLWH and PNLWH, respectively. Regarding regression models, obesity (OR= 7.81; 95%CI: 2.165 – 28.211; p= 0.002) and sedentary behavior (OR= 1.07; 95% CI: 1.002 – 1.156; p= 0.042) rises de odds for be at risk of sarcopenia, while physical exercise (OR= 0.347; 95% CI: 0.131 – 0.914; p= 0.032) reduced these odds. In the multiple models, these factors were not significant. In adjusted models for SarQoL® overall score, sleep quality (OR= 7.343; 95% CI: 3.261 – 16.536; p< 0.001) and obesity (OR= 4.945; 95% CI: 1.597 – 15.304; p= 0.006) higher the odds for lower SarQoL® score, while physical exercise practice was associated with lower odds (OR= 0.173; 95% CI: 0.080 – 0.375; p< 0.001). Conclusion: The risk of sarcopenia was more frequent in PLWH than in PNLWH. Likewise, PLWH showed a lower sarcopenia-related quality of life. Poor sleep quality and obesity increase the odds of lower sarcopenia-related quality of life, while physical exercise diminishes the odds for both PLWH and PNLWH.

Keywords: HIV; Sarcopenia risk; Sarcopenia-related quality of life; age; lifestyle.

Introduction

Given the advancement and improvement of antiretroviral therapy (ART), people living with the human immunodeficiency virus (PLWH) have modified their epidemiological trajectory since the 1990s; they have currently experienced longer life expectancy, mainly due to a drastic reduction in the acquired immunodeficiency syndrome (AIDS) [1-3]. Despite these significant achievements, PLWH still lives with many health-related issues [1]; the residual effect of the virus and many side effects of the ART lead the PLWH to a state of low-grade systemic inflammation (LGSI) [4, 5], which can be associated several chronic conditions [6, 7]. LGSI leads to metabolic and cellular disturbances that negatively impact multiple organs and tissues, including skeletal muscle (SkM) [8, 9]. The ART-related adverse effects can turn mitochondria dysfunctional, increasing insulin resistance and blunting muscle protein synthesis [9-11]. Therefore, these effects can compromise the SkM quality and quantity, which means reductions in muscle mass and strength [12, 13].

Reduced muscle mass and strength are defined as sarcopenia, a recognized muscle disease categorized as primary and secondary. Primary sarcopenia is age-related, while the secondary is interconnected to other disorders, lower physical activities level, LGSI, and other factors [14]. In PLWH, the LGSI is a critical pathway to be at risk of sarcopenia [15]; therefore, secondary sarcopenia is a factor to be considered in this group. Despite this biological plausibility, epidemiological data on sarcopenia in PLWH, particularly after the ART era, are still few and relatively controversial [11, 16-24]. Still, although the criteria for defining sarcopenia are well defined, the tools required are expensive and poorly accessible to clinicians. This implies the need to use questionnaires that allow assessments in larger samples. However, sensitivity, specificity, and predictive value are questioned [25-27].

Besides living with HIV as a critical factor to be a potential candidate to develop sarcopenia, being older, presenting high adiposity, having chronic diseases, sedentary behavior, appetite loss, and consequent unintentional weight loss, excessive alcohol intake and smoking, and poor sleep habits rises de likelihoods to live at sarcopenia risk, develop this disease and exhibit a poor quality of life from sarcopenia [13, 25-28]. In contrast, daily physical exercise practice is a critical protector factor against sarcopenia [13, 25-28]. Moreover, during the COVID-19 social distancing period, several lifestyle related-factors were modified, leading to several health-related concerns affecting daily habits. Considering the necessity to screen for sarcopenia risk, comparing the difference and associated factors between PLWH and non-infected people is required for early interventions and a better prognosis. As such, in this survey, we have two purposes. First, we aimed to screen for the risk of sarcopenia and sarcopenia-related quality of life in people living with and without HIV. Second, we aimed to verify associated factors to be at risk of sarcopenia and lower sarcopenia-related quality of life in PLWH.

Methods

Study type, recruitment, and sample characteristics

We conducted a web-based survey, descriptive, exploratory, cross-sectional, with a non-probabilistic sample composed of two groups of participants. The first one included PLWH using different types of ART, invited from a university-based clinic from São Paulo City, SP, Brazil; the invitation was made from a web messaging application. The second group included non-infected people (PNLWH), invited by social media, using the "snowball sampling" strategy [29]. Criteria to be included in the study for both groups were 18 or more years old, of any gender, residents of the state of São Paulo, Brazil, and

free of Hepatitis C, chronic kidney disease, or cancer. Data were collected between August and December 2021.

Ethical procedures

The Ethical Committee of the University of São Paulo, SP, Brazil, approved the study (protocol number: 4.938.460). All the participants signed a consent form, included on the first page of the online questionnaire.

Questionnaire

The participants responded to the questionnaire via a commercial platform (SurveyMonkey®). The survey consisted of 112 questions, with an average response time of 20 minutes. The main aspects investigated related to our study included sarcopenia risk, sarcopenia-related quality of life, and possible associated factors [26, 30-33], namely: -physical exercise practice; sedentary behavior; sleep problems; the presence of non-communicable diseases; body weight, and recent body weight loss; appetite loss; drinking and smoking habits; age, sex, income, and educational status.

Outcomes (dependent variables)

Sarcopenia risk

We identified people at risk of sarcopenia using the SARC-F, a tool developed by Malmstrom and Morley [34] and validated by Malmstrom et al. [35]. This scale adopts five questions related to some phenotypical aspects of sarcopenia. The maximum score of SARC-F is 10, and scores ≥ 4 indicate persons at risk of sarcopenia.

Sarcopenia-related Quality of Life

We adopted the SarQoL® scale, a tool developed and validated by Beaudart et al. [36], to identify the sarcopenia-related quality of life. The SarQoL® is an easy-to-apply questionnaire that can be self-administered. The questionnaire is available in multiple

languages from the website www.sarqol.org. The SarQoL® consists of 22 questions, each graded on four-point Likert-type scales (often, sometimes, rarely, never) and intensity (very, moderately, a little, and not at all), covering the seven main sarcopenia-associated dimensions: physical and mental health, locomotion, body composition, functionality, activities of daily living, activities of leisure and fear. The total SarQoL® score ranges from zero (worst condition) to 100 (best condition). The Overall QoL score was calculated with the help of the Access database developed for this purpose [37].

Independent variables

Physical exercise and sedentary behavior

Participants described the type and duration of physical exercises if predominantly endurance activities [e.g., walking (except for work) or running, cycling, swimming, spinning, step, jumping, team sports such as futsal/soccer, volleyball, basketball, and handball, fighting, dance class] or strength activities (e.g., weight training, CrossFit®, functional exercise, pilates or calisthenics).

The sedentary behavior was identified from the following questions: *how many hours you spend sitting watching television per day during weekdays and weekends*, and *how many hours you spend sitting on your video game, cell phone, tablet, computer, or other devices per day during weekdays and weekend days*. We summed the reported values (in hours) for each question on weekdays and weekends.

Sleep quality

Sleep issues were investigated using the Mini-Sleep Questionnaire (MSQ), which was developed by Zoomer et al. [38] and translated and adapted to Portuguese by Falavigna et al. [39]. The MSQ contains ten items and assesses sleep quality and daytime sleepiness. The questionnaire score ranges from zero to 60 points, classifying the sleep

pattern into very good sleep (0-9 points), good sleep (10-24 points), slightly altered sleep (25-27 points), sleep moderately modified (28 – 30 points) and significantly altered sleep (above 30 points).

Body weight, diseases, and other health-related questions

The participants described their current body weight and height (which we used to calculate the body mass index, BMI). We asked about weight loss with the question, "*have you lost more than 3 kg unintentionally in the last few months?*" and about appetite, "*have you been experiencing loss of appetite?*" Still, we asked about the presence of chronic diseases diagnosed by a physician [type 1 and 2 diabetes mellitus (DM), systemic arterial hypertension (SAH), or dyslipidemia]. Drinking alcohol habits were answered as: (i) I never drink; (ii) = Less than 1x/month; (iii) = 1 x or more/month. Smoking habits were answered as (i) I do not currently smoke; (ii) yes, daily; (iii) yes, less than daily.

Adjusting Variables

Sociodemographic characteristics

We asked about age (in years), sex at birth (male or female), formal education level (basic, high school, college or more), and monthly income.

Statistical analysis

The Shapiro-Wilk test investigated data normality. Continuous and normally distributed data are presented as mean and standard deviation, while continuous and non-parametric data are presented as the median, minimum, and maximum values. The categorical data are presented as absolute and relative frequency. The groups (PLWH and PNLWH) were compared according to the type of distribution using Independent

Student's t-test or Mann-Whitney test for continuous parametric and non-parametric data, respectively. For categorical variables, we adopted the Chi-square test.

To investigate associations between each variable and outcomes (SARC-F and SarQoL®), we performed logistic regression models, considering the dichotomous nature of the SARC-F and attributing a dichotomous feature to the SarQoL® score (below and above the median).

Thus, for the logistic regression models, SARC-F was treated as a dichotomous variable, with $\geq$ 4 points at risk for sarcopenia. Moreover, worse sarcopenia-related quality of life was defined as below the median.

The models were constructed in three steps, as follows.

First step: We performed simple regression models taking each independent variable, being: living with HIV, DM, SAH, high cholesterol levels (all yes vs. no), recent weight and appetite loss (both yes vs. no), BMI (obese and overweight vs. normal weight), exercise practice (yes vs. no), sedentary behavior by time in front of the TV, tablet and other devices (continuous), sleep-related problems (good sleep quality vs. poor sleep quality).

Second step: To be included in multiple models, the variables tested in the single models should fit the following criteria: (i) p-value $<$ 0.20; (ii) absence of multicollinearity analyzed by the variance inflation factor (VIF) and tolerance when inserted in multiple models. The multiple models considered the variable significant when the p-value was $\leq$ 0.05.

Third step: In the multiple models created, age (continuous), sex (male vs. female), schooling level (until high school vs. college or more), and monthly income (until 2 Brazilian minimum wages vs. more) were inserted as adjusted variables. The adjusted models considered the variable significant when the p-value was $\leq$ 0.05. All

statistical tests were performed with JAMOVI® version 2.2.5 Solid Version for macOS. The Software G*Power estimated the sample power *a posteriori*.

Results

The non-probabilistic survey generated 536 responses; however, after curating the data, 344 participants were included in the final data file [189 men (150 PLWH and 39 PNLWH) and 155 women (61 PLWH and 94 PNLWH)]. Table 1 depicts the main characteristics of the whole sample and according to the HIV presence. The PLWH group was older than PNLWH, predominantly male, and with a higher percentage of homosexual participants. The PLWH referred to poorer sleep quality, lower frequency of practicing any exercise, and increased time in front of the TV compared with PNLWH. They referred to a shorter time using mobile phones, computers, and others. The BMI, recent body weight loss and recent appetite loss did not differ between groups. Considering only PLWH, the SARC-F identified 10.43% (95 % CI: 6.6 – 15.4%) at risk of sarcopenia; in turn, regarding only PNLWH, only one was at risk of sarcopenia (0.75%; 95% CI: 1.90e-4 – 4%). Regarding SarQoL® overall score, PLWH exhibit lower score than PNLWH ($p = 0.003$).

Insert table 1

Table 2 depicts the results stratified by the SARC-F questionnaire. Regarding $\geq$ 4 cutoffs at risk of sarcopenia, 23 and 22 of the whole sample and PLWH were at sarcopenia risk, respectively. Taking into account only PLWH, BMI, sedentary behavior, and poor sleep quality were higher in people at sarcopenia risk when compared to people without sarcopenia risk. Besides, people at sarcopenia risk showed a lower SarQoL® overall score than people without sarcopenia risk.

Insert Table 2.

Table 3 depicts the logistic regression model considering SARC-F as a dependent variable. Thus, since only one person of PNLWH is at risk of sarcopenia, this model was constructed only with PLWH. Sample power was estimated considering proportions observed for sarcopenia risk (10,43% of PLWH), the odds ratio of these proportions (0,013), alpha error of 5%, and sample size (n= 211 of PLWH). The power estimated was 0,99.

Sedentary behavior by watching TV (1.07; 95% CI 1.002 – 1.156; p = 0.042) and being obese (7.81; 2.165 – 28.211; p = 0.002) augmented the odds of be at risk of sarcopenia; however, in contrast, physical exercise practice decreases the odds (0.347 (0.131 – 0.914; p = 0.032). However, these factors were significant only in univariate analyses.

Insert Table 3.

Table 4 displays the logistic regression model considering SarQoL® overall score as a dependent variable. Sample power was estimated considering the proportions of independent variables (n= 14), lower proportion observed (44,5% of lower SarQoL®), alpha error of 5%, and power of 80 %. The estimated sample size needed was 315.

In the adjusted model poor sleep quality (7.343; 95% CI: 3.261 – 16.536; p < 0.001) and obesity (4.945; 95% CI: 1.597 – 15.304; p = 0.006) increased the odds for lower sarcopenia-related quality of life. In contrast, physical exercise practice (0.173; 95% CI: 0.080 - 0.375; p < 0.001) was the most protector factor for lower sarcopenia-related quality of life. In disagreement with our initial hypothesis, living with HIV was not associated with lower sarcopenia-related quality of life by SarQoL® questionnaire.

Insert table 4.

Discussion

The first purpose of this survey was to identify the prevalence of living at risk of sarcopenia in PLWH and PNLWH and their sarcopenia-related quality of life. Second, we aimed to verify associated factors to be at risk of sarcopenia and lower sarcopenia-related quality of life in PLWH.

First, sarcopenia risk was higher in PLWH than in PNLWH. Moreover, PLWH exhibit a lower score for quality of life than PNLWH. In PLWH, poor sleep quality and obesity increase the odds of being at risk of sarcopenia, and only physical exercise decrease the odds. Nevertheless, these factors were only significant in univariate analysis. In multiple adjusted models, they are not significant. Regarding the sarcopenia-related quality of life, in adjusted multiple models, sleep problems and obesity increase the odds of a lower SarQoL® score. In contrast, physical exercise decreases the odds of a lower SarQoL® score.

To our knowledge, it is the first survey that applied SARC-F and SarQoL® questionnaires in PLWH. Previous studies showed that PLWH had higher odds of sarcopenia [40-42]. For instance, Oliveira et al. [43] observed that sarcopenia prevalence was 24.1%; besides, studies comparing PLWH with PNLWH show an 11.1% of sarcopenia prevalence, adopting different diagnosis criteria [41, 42, 44-48]. Nevertheless, PLWH had 2.4 greater odds of sarcopenia than non-infected persons.

The hypothesis that HIV affects SkM is mainly related to higher inflammatory mediators derived from several compartments [4]. For instance, living with HIV impairs gut mucosal T cells, particularly $CD4^+$ Th17 cells, affecting gut microbiota composition, decreasing mucus thickness, and augmenting gut permeability. These gut changes allow the translocation of inflammatory molecules, such as lipopolysaccharide, that are recognized for cells and tissues and trigger inflammatory pathways [49].

Adverse ART-associated effects from different drugs disturb lipid and muscle metabolism due to mitochondrial dysfunction, which lowers fatty acid oxidation capacity [50, 51]. Previous studies showed that fat redistribution associated with HIV increases visceral fat [52]. Besides, PLWH increases ectopic lipid accumulation in tissues such as SkM [52-54]. Higher SkM ectopic fat deposition activates pro-inflammatory pathways, activating inflammasomes and increasing the synthesis of pro-inflammatory cytokines [55, 56]. This condition increases insulin resistance and opens windows to develop anabolic resistance, modifying the muscle quality and quantity [56]. Some published cohorts showed lower muscle density in PLWH due to increased fatty acid infiltration into SkM [11, 21].

Nucleoside reverse transcriptase inhibitors (NRTIs), especially thymidine analogs, are the most lipoatrophy-related class of drugs associated with mitochondrial toxicity [57]. Also, some protease inhibitors are involved in visceral fat expansion, dysfunction, and consequent insulin resistance [50, 58]. Although some new-generation ART drugs are pointed to generate lower mitochondrial damage than the previous drugs [59, 60], unfavorable side effects have still been identified [61, 62]. For instance, lamivudine impairs the efficiency of adipose tissue mitochondria [62], and the combination of tenofovir and lamivudine reduces the electron transport chain activity in adipose tissue's mitochondria [63]. Moreover, dolutegravir has been associated with fat gain, reinforcing the hypothesis of higher SkM fatty acid infiltration [64, 65].

Concerning SarQoL® results, we verified that overall scores were lower in PLWH than in PNLWH. Likewise, people at risk of sarcopenia presented a lower overall SarQoL® score. Our data suggest that PLWH at sarcopenia risk exhibit an overall SarQoL® score similar to or smaller than those aged adults with sarcopenia, reinforcing the hypothesis of anticipated age of PLWH. Beaudart et al. [66] verified that the SarQoL®

of people living with sarcopenia was worse than people without sarcopenia. This comparison was performed considering low muscle mass and muscle functions sarcopenia definition [67-70]. The relationship between SkM-related parameters and PLWH QoL was poorly explored, but studies have documented that lower muscle mass was negatively associated with QoL in the general population [71].

Our results revealed that physical exercise was a protector factor for lower SarQoL® overall score. Although it is unquestionably that physical exercise practice is indispensable to health maintenance, only 50% of PLWH meets physical exercise recommendations [72]. Endurance and resistance exercise improves the body composition of PLWH [73]. Likewise, Pérez-Chaparro et al. [74] observed that physical exercise was associated with better QoL of PLWH. It is well accepted that muscle disuse promotes negative changes in body composition, reductions in muscle strength and quality, anabolic resistance, and poor glycemic control [75].

In a scoping review, Chetty et al. [76] described and analyzed several studies that identified the physical exercise effects on cardiorespiratory capacity, strength, and QoL of PLWH. They observed that endurance and resistance exercises improved several health parameters and ameliorated HIV-related disorders. Specifically, resistance exercise can improve sarcopenia-associated parameters such as upper and lower body strength, balance, flexibility, and functionality. More recently, Ghayomzadeh et al. [77] submitted PLWH to three times a week resistance exercise for six months. Appendicular lean mass, grip strength, and gait speed improved in resistance exercise compared to the control group. Moreover, inflammatory parameters (i.e., interleukin-6 and TNF-α) decreased in the resistance exercise group, while IGF-1 levels increased. They also observed a negative correlation between IL-6 and grip strength, TNF-α, and grip strength, reinforcing the hypothesis of low-grade inflammation.

We verified that low sleep quality increased the odds of low SarQoL® overall score, and previous data indicated that PLWH displays poor sleep-related parameters. Several pathophysiological HIV-associated factors may cause sleep-wake dysregulation [78, 79]. For instance, immune activation contributes to insomnia and obstructive sleep apnea syndrome [80]. Moreover, HIV-associated neurocognitive disorders affect dopaminergic signaling, increasing wakefulness and worsening the rapid eye movement and slow-wave sleep quality [81]. It is believed that poor sleep-related parameters contribute to hormonal dysregulation, suppressing molecular pathways involved in SkM protein synthesis; consequently, muscle mass and strength get worse [26, 82-84]. Nonetheless, more studies are needed to elucidate this relationship, especially in PLWH. Finally, living with obesity was associated with a higher chance of a lower SarQoL® overall score. The increase in body adiposity may favor several changes related to worsening SkM function. The main ones are increased fat infiltrates, which trigger inflammation pathways related to insulin and anabolic resistance [85]. Physical inactivity contributes to increased body adiposity and SkM metabolic inefficiency [86]. Also, several alterations in lipid metabolism are reported in PLWH, significantly increased central fat with more powerful inflammatory potential [57].

Our study has some limitations. The cross-sectional design makes it impossible to infer causal relationships. Also, this web-based survey included only subjective descriptions to assess sarcopenia risk and sarcopenia-related QoL. This study presented some limitations, such as (i) age and sex of groups were significantly different; for this reason, these factors were included in the regressions model; (ii) this is a cross-sectional survey and is unable to infer causality; (iii) PLWH presents a less social and life scenario compared to PNLWH. This factor is unlikely to be controlled for in multiple models since measuring the stigma, and the burden of social problems PLWH faces is complex and

(iv) The sample power and size were estimated *a posteriori*. On the other hand, our work has strengths as the innovative simultaneous application of SARC-F and SarQoL® in PLWH. As far as we know, this is the first study that evaluated and compared sarcopenia risk and sarcopenia-related QoL in PLWH. We conclude that the PLWH presented a higher risk of sarcopenia, and the lower sarcopenia-related quality of life is higher in PLWH than in PNLWH. Also, poor sleep quality and obesity higher the odds to lower sarcopenia-related quality of life. In contrast, physical exercise is a protector factor for the lower sarcopenia-related quality of life.

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Conflicts of interest

All the authors declare no conflicts of interest.

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Tables.

Table 1. Features of the whole sample and according to the HIV condition. São Paulo, Brazil, 2021.

Variable	Whole sample mean/median (SD/IQR) or n (%)	PLWH mean/median (SD/IQR) or n (%)	PNLWH mean/median (SD/IQR) or n (%)	p-value
Sample size (n)	344	211	133	
Age (years)	45.5 (13.1)	52.3 (8.62)	34.7 (11.5)	**<0.001**
Sex				
Male	189 (54.94)	150 (71.10)	39 (29.32)	**< 0.001**
Female	155 (45.05)	61 (28.90)	94 (70.68)	
Age (years)	45.5 (13.1)	52.3 (8.62)	34.7 (11.5)	**< 0.0001**
Age groups				
18 – 29	55 (16.36)	2 (0.97)	53 (40.45)	**< 0.0001**
30 – 35	38 (11.31)	4 (1.95)	34 (25.95)	
36 – 40	34 (10.12)	19 (9.27)	15 (11.45)	
41 – 45	27 (8.03)	17 (8.29)	10 (7.63)	
46 – 50	45 (13.39)	41 (20)	4 (3.05)	
51 – 55	57 (16.96)	53 (25.85)	4 (3.05)	
56 – 60	45 (13.39)	40 (19.51)	5 (3.81)	
≥ 61	35 (10.41)	29 (14.14)	6 (4.58)	
Sexual orientation				
Heterosexual	190 (55.23)	81 (38.39)	109 (81.95)	**< 0.001**
Homosexual	115 (33.43)	106 (50.23)	9 (6.76)	
Bisexual	28 (8.13)	15 (7.10)	13 (9.77)	
Other	2 (0.58)	1 (0.47)	1 (0.75)	
Sleep Quality (Score)	31.2 (9.98)	32.2 (10.1)	29.6 (9.55)	**0.027**
Sleep Quality (Categories)				

Very good sleep	78 (26.5)	43 (23.37)	35 (31.82)	**0.036**
Good sleep	35 (11.9)	17 (9.24)	18 (16.36)	
Slightly altered sleep	39 (13.3)	24 (13.04)	15 (13.64)	
Very altered sleep	142 (48.3)	100 (54.35)	42 (38.18)	
Exercise practice				
Not performed	111 (37.4)	78 (41.93)	33 (29.73)	**<0.001**
Strength	62 (20.9)	41 (22.04)	21 (18.92)	
Endurance	71 (23.9)	49 (26.34)	22 (19.82)	
Both	53 (17.8)	18 (9.67)	35 (31.53)	
Sedentary behavior				
Sitting time watching TV (h)	6.76 (5.19)	7.40 (5.61)	5.68 (4.20)	**0.006**
Sitting time on cell phone, video game or computer (h)	8.59 (5.87)	7.47 (6.00)	10.5 (5.14)	**<0.001**
BMI (kg/m^2)	25.7 (5.07)	25.9 (4.01)	25.3 (6.20)	0.206
Recent weight loss				
Yes	31 (10.84)	18 (10.53)	13 (11.30)	0.836
No	255 (89.16)	153 (89.47)	102 (88.70)	
Recent appetite loss				
Yes	17 (12.78)	8 (10.81)	9 (15.25)	0.446
No	116 (87.22)	66 (89.19)	50 (84.75)	
SARC-F				
0 - 3	321 (93.31)	189 (89.57)	132 (99.25)	**<0.001**
≥ 4	23 (6.69)	22 (10.43)	1 (0.75)	
SarQoL® *Overall* score	78.5 (5.88 – 100)	76.5 (5.88 – 98.1)	83.2 (5.88 – 100)	**0.003**

Legend: Data are presented as mean, median, standard deviation, minimum max, absolute, and relative frequency. **BMI:** Body Mass Index. Independent t-test and Mann-Whitney test were performed for continuous parametric and nonparametric data, respectively. Chi-square was performed to verify differences in the frequency distribution. Significant differences were considered when the p-value was less than or equal to 0.05. Analyses were performed with JAMOVI® version 2.2.5 Solid Version for macOS.

Table 2. SarQoL® results of people living with and without sarcopenia risk, considering the whole sample and the PLWH group. São Paulo, Brazil, 2021.

	Whole sample			**PLWH**		
Variable	**Sarcopenia risk (n = 23)**	**Without sarcopenia risk (n = 321)**	**p-values**	**Sarcopenia risk (n = 22)**	**Without sarcopenia risk (n= 183)**	**p-values**
Age (years)	49.3 (8.9)	45.2 (13.3)	0.144	50.4 (7.27)	52.6 (8.76)	0.274
BMI (kg/m^2)	27.8 (5.4)	26.2 (4.58)	0.103	28.2 (5.35)	26.1 (3.87)	**0.024**
Sleep quality score	44.5 (10.2)	30.2 (9.22)	**<0.001**	44.2 (10.3)	30.7 (9.09)	**<0.001**
Sedentary behavior (hours in front TV)	9.60 (8.74)	6.55 (4.7)	**0.011**	9.97 (8.81)	7.10 (5.07)	**0.035**
Sedentary behavior (hours in front other devices)	9.09 (7.71)	8.56 (5.73)	0.698	8.83 (7.83)	7.32 (5.76)	0.300
SarQoL® Overall score	50.4 (16.7 – 68.9)	80.1 (5.88 – 100)	**<0.001**	50.5 (16.7 – 68.9)	78.6 (5.88 – 100)	**<0.001**

Legend: Data are presented median, minimum max. Mann-Whitney tests were performed for continuous nonparametric data. Significant differences were considered when the p-value was less than or equal to 0.05. Analyses were performed with JAMOVI® version 2.2.5 Solid Version for macOS.

Table 3. Regression models with PLWH and risk of sarcopenia as dependent variable. São Paulo, Brazil, 2021.

	Crude model		Multiple model		Adjusted model[a]	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Physical Exercise	**0.347 (0.131 – 0.914)**	**0.032**	0.311 (0.043 – 2.250)	0.247	0.565 (0.027 – 11.710)	0.712
Sitting watching TV	**1.07 (1.002 – 1.156)**	**0.042**	0.973 (0.849 – 1.110)	0.695	1.027 (0.828 – 1.270)	0.808
Overweight	1.706 (0.503 – 5.784)	0.391	0.893 (0.148 – 5.380)	0.902	0.182 (0.005 – 5.740)	0.333
Obese	**7.81 (2.165 – 28.211)**	**0.002**	1.261 (0.092 – 17.240)	0.862	0.411 (0.012 – 13.200)	0.615
Recent weight loss	2.629 (0.766 – 9.014)	0.124	3.039 (0.265 – 34.840)	0.372	4.469 (0.016 – 20.731)	0.600
Living with DM	2.353 (0.786 – 7.037)	0.126	1.188 (0.080 –17.600)	0.900	0.342 (0.024 – 46.109)	0.631
Recent appetite loss	3.333 (0.547 – 20.307)	0.192	4.081 (0.224 – 74.150)	0.342	0.987 (0.002 – 29.430)	0.996

BMI: Body Mass Index; Logistic regression performed with JAMOVI® version 2.2.5 Solid Version for macOS. For overweight and obese categories normal weight was reference; a = model was adjusted by age, sex, schooling level, socioeconomic status, and smoking habits.

Table 4. Regression models with PLWH and PNLWH considering sarcopenia-related quality of live as dependent variable. São Paulo, Brazil, 2021.

	Crude model		Multiple model		Adjusted model[a]	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Living with HIV (living without HIV is reference)	1.679 (1.083 – 2.60)	**0.020**	1.516 (0.715 – 3.209)	0.277	0.742 (0.227 – 2.425)	0.621
Sleep quality (good sleep is reference)	5.090 (2.984 – 8.682)	< **0.001**	7.135 (3.489 – 14.593)	< **0.001**	7.343 (3.261 – 16.536)	< **0.001**
Physical Exercise (no exercise practice is reference)	0.205 (0.123 – 0.339)	< **0.001**	0.168 (0.084 – 0.335)	< **0.001**	0.173 (0.080 – 0.375)	< **0.001**
Sitting watching TV	1.051 (1.004 – 1.101)	**0.033**	1.043 (0.978 – 1.111)	0.197	1.047 (0.977 – 1.122)	0.191
High cholesterol levels	2.228 (1.423 – 3.489)	<**0.001**	1.677 (0.810 – 3.467)	0.163	0.908 (0.385 – 2.138)	0.825
Overweight	1.080 (0.663 – 1.759)	0.756	1.447 (0.723 – 2.895)	0.296	2.106 (0.931 – 4.763)	0.073
Obese	3.248 (1.661 – 6.349)	<**0.001**	3.635 (1.347 – 9.811)	**0.011**	4.945 (1.597 – 15.304)	**0.006**
Recent weight loss	2.321 (1.068 – 5.04)	**0.033**	2.751 (0.988 – 7.657)	0.053	2.292 (0.735 – 7.142)	0.152
Living with DM	2.376 (1.089 – 5.18)	**0.030**	0.828 (0.233 – 2.932)	0.770	0.620 (0.273 – 1.438)	0.500

BMI: Body Mass Index; Logistic regression performed with JAMOVI® version 2.2.5 Solid Version for macOS. For overweight and obese categories normal weight was reference; a = model was adjusted age, sex, schooling level, socioeconomic status, smoking habits.

6.3 Artigo 3 – Sarcopenia in people living with HIV and associated factors: a cross-sectional study

Sarcopenia in people living with HIV and associated factors: a cross-sectional study

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Abstract

Antiretroviral therapy (ART) improves life expectancy for people living with the human immunodeficiency virus (PLWH). However, HIV- and ART-related side effects could lead to chronic disorders, such as sarcopenia, a muscle disease defined by lower muscle strength and mass. Thus, we aimed to identify sarcopenia prevalence and compare sarcopenia-related components between PLWH and not living with HIV (PNLWH). Besides, we aimed to verify factors associated with sarcopenia-related components in PLWH. We conducted a cross-sectional study with a non-probabilistic sample composed of two groups of participants: PLWH with undetectable viral load (< 50 copies/mL) under ART and PNLWH. Data were collected between August 2021 and May 2022. Sarcopenia-associated components (i.e., muscle strength, and muscle mass) were evaluated by handgrip strength (HGS) and Dual-energy x-ray absorptiometry (DXA). From DXA, we calculate the appendicular lean mass index (ApLMI). Lower HGS and ApLMI were considered to be sarcopenic. We applied the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) and Sarcopenia Definition and Outcomes Consortium (SDOC) sarcopenia cutoff. Moreover, from fat mass (FM), we calculate the FM index (fat mass divided by squared height; FMI) and fat: lean mass ratio (total fat mass divided by lean mass). Moreover, the muscle quality index (MQI_{total}) was obtained by dividing HGS by ApLM. Other health issues were collected, such as HIV diagnosis duration, current ART regimen, and previous ART-related drugs associated with poor muscle quality (i.e., zidovudine, stavudine, and ritonavir). The total sample included 70 participants (45.5±7.73 years; n= 35 PLWH). Considering the EWGSOP2 cutoff, both PLWH and PNLWH were not sarcopenic. Only by SDOC cutoff one (2.86%) PNLWH as sarcopenic. Regarding dynapenia (isolate lower HGS) by EWGSOP2, one (2.86%) and seven (20%) PNLWH and PLWH were dynapenic (p= 0.024), respectively. By SDOC nine (25.7%) and twenty-one (60%) PNLWH and PLWH were dynapenic (p= 0.004), respectively. We verified that PLWH exhibited lower HGS (-6.68 kg; p= 0.005), and MQI_{total} (-0.393 kg/kg; p= 0.005), without differences in ApLMI (-0.138 kg/m^2; p= 0.641). Furthermore, FM: LBM ratio (ß= -15.476; p< 0.001) and living with HIV (ß= -7.966; p< 0.001) were negatively associated with HGS. In contrast to our hypothesis, living with HIV was modest but positively associated with ApLMI (ß= 0.584; p= 0.040). Regarding ART, ritonavir was negatively associated with HGS (ß= -6.143; p< 0.001) and zidovudine was positively associated with FMI (ß= 2.71; p= 0.038) and FM: LBM ratio (ß= 0.146; p= 0.037). In conclusion, PLWH presented a higher prevalence of dynapenia, lower HGS, and MQI_{total} than PNLWH. Also, FM: LBM ratio, living with HIV, and ritonavir's previous utilization were negatively associated with HGS, and previous zidovudine use was positively associated with FMI and FM: LBM ratio. Studies with higher sample sizes and longitudinal design must confirm our findings.

Keywords: HIV. Antiretroviral. Sarcopenia. Muscle strength. Skeletal muscle.

Introduction

The human immunodeficiency virus (HIV) is responsible for Acquired Human Immunodeficiency Syndrome (AIDS) and has been the most studied virus in the last four decades. Since the beginning of the HIV epidemic in the 1980s, 36.3 million people have died from AIDS-associated causes [1]. These deaths were caused mainly due to the absence of efficient treatments. However, with the advent and improvement of antiretroviral therapies (ARTs), it has been possible to control HIV replication, which contributed to the significant decrease of AIDS-related mortality over the last decades [2-6].

ARTs provided a new epidemiological scenario to the history of HIV, increasing the life expectancy of the infected people [2]. Globally, 5.7 million people aged ≥ 50 years were living with HIV in 2016, which was three times higher than in the 2000s. In 2020, this number increased to approximately 7.5 million. In Brazil, approximately one million people were living with HIV in 2020; of these, it is estimated that 650 thousand people living with HIV (PLWH) are using ART [1, 7].

Despite the unquestionable positive effects of ARTs in controlling the viral load, several studies have shown residual HIV- and ART-related metabolic disturbances as side effects (i.e., insulin resistance, mitochondrial toxicity)[8]. Persistent immune activation and low-grade systemic inflammation (LGSI) have emerged as the main factors associated with these disturbances, which increases the risk of developing non-AIDS diseases [9-13]. Although ARTs can reduce viral load to undetectable levels, they do not entirely suppress immune activation by immune cells [14]. Besides, HIV accessory proteins (i.e., Tat, Vpr, and Nef) can diminish mitochondrial efficiency in white adipose tissue (WAT), increasing the oxidative stress and systemic inflammation [15]. Likewise, lymphocytes express more C-X-C chemokine receptor type 5 (CXCR-5) in the intestine, increasing the synthesis of gut inflammatory mediators. Also, changes in the gut microbiota (i.e., higher abondance of Prevotella gender and fewer abundance of Bacteroides and other butyrate-producing bacteria) lead to lower concentration of Th17 lymphocyte subtype, increasing intestinal permeability and the translocation of inflammatory mediators such as lipopolysaccharide (LPS) to the bloodstream, [16-22].

These mechanisms sustained by LGSI in PLWH contribute to the hypothesis of aging anticipation [23, 24]. Inflammatory mediators could reach skeletal muscle (SkM), trigger catabolic pathways (i.e., ATP-Dependent Ubiquitin-Proteasome, Calpains,

Autophagy, Apoptosis), and slow down anabolic pathways (mainly the mTORC1-related), leading to muscle diseases, such as sarcopenia [25, 26] or dynapenia. *Sarcopenia* is a muscle disease defined by reduced muscle strength and mass, while *dynapenia* is the loss of muscle strength [27-29]. However, it is difficult to identify the prevalence of these conditions because different methods and criteria are applied to assess sarcopenia-related factors in PLWH's studies [30]. In addition, few studies investigated the factors associated to the sarcopenia components [31]. Therefore, we aimed to identify sarcopenia prevalence and compare sarcopenia-related components between PLWH and PNLWH. Moreover, we aimed to verify factors associated with sarcopenia-related components in PLWH.

Methods

Study type, recruitment, and sample characteristics

This is a cross-sectional, descriptive, and exploratory survey with a non-probabilistic sample, composed by two groups of participants: PLWH and non-infected persons (PNLWH). Previously to the development of the present study, we conducted a web-based survey (study submitted to publication) with persons with the same characteristics (PLWH and PNLWH). Those who manifested interest in participating in this step were recruited. The recruitment of each PNLWH was matched to a PLWH, according to sex and age.

For both groups, criteria to be included in the study were being ≥18 years old, being male or female, residing at the state of São Paulo, Brazil, and being free of Hepatitis C, chronic kidney disease, or cancer. Still, PLWH needed to have an undetectable viral load (< 50 copies/mL) and to be under any ART therapy. Data were collected between August 2021 and May 2022.

Ethical procedures

The Ethical Committee of the University of São Paulo, SP, Brazil approved the study (protocol number: 4.938.460) and all the participants signed a consent form.

Outcomes (dependent variables)

Muscle Strength

We evaluated muscle strength with a Jamar® handgrip strength (HGS) dynamometer. This dynamometer features a static indicator for easy reading, with a 0 – 90 kg scale and a resolution of 2 kg. Grip strength was measured in both hands in a seated position with the arm at a 90-degree angle, according to the National Health and Nutrition Examination Survey (NHANES) guidelines for hand dynamometry. Handgrip strength was measured three times, with 1-minute interval between measurements, and the highest score was used for each hand [32].

Body composition

We used Dual-energy x-ray absorptiometry (DXA) to assess body composition (Lunar iDXA, GE Healthcare, with incore Software Platform). DXA is relatively inexpensive, with short scan times and low radiation exposure. The participants were placed in a supine position on the machine's stretcher with arms pronated and feet in dorsiflexion. An X-ray source above the volunteer emitted photons at two distinct energy levels, specific for soft tissue and cortical bone. A collimator is situated between the patient and the X-ray source to mitigate the emission. The attenuations from these low and high-energy photon emissions were detected and were combined to create a planar image to assess body composition.

Participants were instructed to arrive at the laboratory in the morning with empty stomach, without performing strenuous physical exercises the day before, and with light clothing, without metals. Data used in this study included total fat mass (FM; kg and %), total lean body mass (LBM; kg), arms FM and lean mass; legs FM and lean mass, ApLM (sum of arms and legs lean mass), ApFM (sum of arms and legs fat mass). We calculate the appendicular lean mass index (ApLMI) from the ApLM divided by the squared height ($ApLM/h^2$) and Fat mass index (FMI) by Fat mass divided by squared height [33].

Sarcopenia and dynapenia-related definitions

We treated the sarcopenia parameters (muscle strength and ApLMI) in three manners, being (i) continuous, to compare PLWH and PNLWH, (ii) considering the

Working Group on Sarcopenia in Older People (EWGSOP) cutoff, to lower muscle strength and mass (HGS: < 27 kg for men and < 16 kg for women and ApLMI: < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women) [28], and (iii) according to Sarcopenia Definitions and Outcomes Consortium (SDOC) cutoff, to lower muscle strength and mass (HGS: < 35.5 kg for men and < 20 kg for women and ApLMI: < 7.26 kg/m^2 for men and < 5.45 kg/m^2 for women) [34]. Lower muscle strength by HGS according to EWGSOP or SDOC cutoffs was defined as dynapenia. The combination of lower HGS plus lower ApLMI, according to EWGSOP or SDOC cutoffs, was defined as sarcopenia. The physical performance by the walking speed test was considered to determine the severity of sarcopenia. Those whose time was < 0.8 m/s, in addition to the other criteria described above, were classified as severe sarcopenia.

Dynapenic obesity and Dynapenic abdominal obesity

To define dynapenic obesity, we considered lower HGS according to EWGSOP and SDOC criteria plus BMI > 30 km/m^2. To define dynapenic central obesity, we considered lower HGS plus waist circumference > 102 cm for men and > 88 cm for women [35].

Independent variables

Body composition-related parameters

We converted ApLMI and FMI in z-score according to the NHANES reference value from Kelly, Wilson [36] publication. The z-scores can be calculated by the following equation: $Z = \frac{score - mean}{SD}$. Subsequently, we applied ApLMI and FMI to calculate ApLMI adjusted for FMI (ApLMI$_{FMI}$), according to the following steps:

Step 1: We determined the predicted ApLMI Z-Score relative to FMI Z-score using Weber, Long [37] age-, sex-, and ethnicity-appropriate regression analyses.

$$Predicted\ ALMI\ Z\ Score\ =\ \beta 1\ (FMI\ z\ Score)\ +\ \beta 2\ (FMI\ z\ Score)2\ +\ constant$$

Step 2: We generated an ApLMI$_{FMI}$ Z-Score for the individual incorporating the actual ApLMI Z-score from step 1 above and the sex- and ethnicity-appropriate SD using the following equation [37]:

$$ApLMI_{\text{FMI}} = \left(Actual\ ApLMI\ Z\ score - Predicted\ ApLMI\ z\ Score * \left(\frac{1}{SD}\right)\right)$$

Low $ApLM_{FMI}$ was defined when Z ≤ -1.0 SD [37].

Muscle quality

From muscle strength by HGS, we determined muscle quality index (MQI) dividing HGS by ApLM, according to a recent publication by Lopes et al. Our DXA equipment does not offer separated arm lean mass; thus, we chose MQI_{total}, which was defined by HGS (values from dominant + non-dominant hand) divided by ApLM [38].

Physical performance

We analyzed gait speed by the average value of three consecutive trials of 4.6-m walking distance. Four markings were put on the easy-to-walk floor, totalizing 8.6 m. We considered the distance between the first and second markings (2 m) to be the acceleration phase and the distance between the third and fourth markings (2 m) to be the deceleration phase. The speed between markings 2 and 3 (4.6 m) was obtained using a chronometer. We oriented the participants to perform their usual velocity of walk. Gait speed was measured in meters per second (m/s).

Anthropometry, diseases, and other health-related questions

All participants were evaluated with minimum fasting of 4 hours, with light clothes, without shoes, and in triplicate according to the National Health and Nutrition Examination Survey (NHANES) recommendations [39]. Mean value was used for any calculation.

Body weight was measured using a digital balance with a 100 g scale accuracy. Height was measured using a portable stadiometer with 0.1 cm accuracy. The subjects were instructed to stand close to the stadiometer, with their head in the Frankfurt position. Measurement was taken at the end of a deep inward breath. All circumferences were measured with an inelastic tape. Participants were instructed to stand with their arms crossed on the contralateral shoulders and the tape was set at the midpoint between the anterior superior iliac spine and below the last rib to assess waist circumference. Then, the tape was set at the maximal circumference of the gluteal musculature to assess hip circumference. Calf circumference was measured with subjects sitting with the leg at a 90-degree angle. The tape was set at the maximum circumference in the plane

perpendicular to the longitudinal line of the calf. An experienced researcher measured all circumferences.

Body mass index (BMI) was obtained dividing weight by squared height and the classification applied was < 18.5 kg/m^2 to underweight, 18.5 to 24.9 kg/m^2 to normal weight, 25.0 to 29.9 kg/m^2 to overweight, and > 30.0 kg/m^2 to obesity, according to WHO [40]. Still, waist-to-hip ratio was calculated dividing the waist circumference by the hip circumference.

Participants were questioned about the presence of chronic diseases diagnosed by a physician [type 1 and 2 *diabetes mellitus* (DM), systemic arterial hypertension (SAH), dyslipidemia, or gastrointestinal disease]. Alcohol drinking habits were answered as (i) I never drink; (ii) = 1 x or more/month. Smoking habits were answered as (i) I do not currently smoke; (ii) yes, daily I smoke weekly or monthly.

Adjusting Variables

Sociodemographic characteristics

Age (in years), sex at birth (female or male), educational status (primary course, high school, college, postgraduate course [masters or doctorate] or never studied) and ethnicity (white and non-white) were referred by the participants. According to Brazilian's minimum wages, we asked about monthly income: < 1 minimum wage; 1 to 2 minimum wages; 2 to 3 minimum wages; 3 to 4 minimum wages; 5 to 9 minimum wages; 10 or more.

Statistical analysis

The Shapiro-Wilk test investigated data normality. Continuous and normally distributed data are presented as mean and standard deviation, while continuous and non-parametric data are presented as the median, minimum, and maximum values. The categorical data were presented as absolute and relative values. The groups (PLWH and PNLWH) were compared using Independent Student's t-test or Mann-Whitney test, according to the type of distribution. For categorical variables, we adopted the Chi-square test.

To investigate the associations between each dependent variable and outcomes (HGS and ApLMI), we performed linear regression models, considering the gaussian

distribution of both. To evaluate muscle strength by HGS and muscle mass by ApLMI we used absolute values. We calculated ApLM based on the publication of Heymsfield et al. [41]. Thus, ApLMI is derived from the total arms and legs mass minus the amount of fat and bone mass of these limbs, obtained by DXA assessment. ApLMI is the most used skeletal muscle-related parameter to verify muscle mass changes and associated factors in sarcopenia studies [42]. Although previous studies with PLWH have used the EWGSOP consensus [43], other studies use the SDOC definition [44] and most studies defined sarcopenia by low ApLMI (< 2 SD) [45, 46]. Moreover, to verify ApLMI-associated factors in the regression model, we didn't insert muscle-related variables (i.e., LBM, arms', and legs' lean mass or ApLM) for high multicollinearity.

The models were constructed in three steps, as follows:

First step: single models. We performed simple regression models considering HGS and ApLMI as dependent variables.

For HGS, we tested, as independent variables, living with HIV, fat-related (i. e., total FM, arms and legs FM, ApFM, FMI, trunk: ApFM, FM: LBM ratio), and muscle mass-related (LBM, arms and legs LM, ApLM, ApLMI, and Gait speed) variables, age and sex.

For ApLMI, we tested, as independent variables, living with HIV, fat-related (i. e., total FM, arms and legs FM, ApFM, FMI, trunk: ApFM, FM: LBM ratio), and muscle-related function (i. e., HGS and Gait speed) variables, age and sex.

Second step: multiple models. To be included in multiple models 1, the variables tested in the single models must have complied with the following conditions: (i) have biological relevance based on the theoretical assumption related to sarcopenia; (ii) p-value ≤ 0.20; (iii) the absence of multicollinearity analyzed by the variance inflation factor (VIF) and tolerance when inserted in multiple models [47]. For this reason, we verified multicollinearity, especially when fat-related and muscle-related variables were inserted in multiple models. To pick one independent variable to insert into multiple models, we considered the higher beta value and lowered AIC [48].

Step three: adjusting for cofounding variables for HGS and ApLMI such as smoking (non-smoker is the reference), alcohol intake (no-drinker is the reference), educational status (primary education is the reference), income (< 1 to 3 BMW is the reference). In addition, variables that differed in the between-group comparison analysis were inserted to avoid bias in the associations.

Furthermore, regression models were done only with PLHIV, including the variables that were significant in the adjusted multiple models and the information related to ARTs, such as time of disease, duration of treatment, CD4+ nadir, current ART regimen [INTR associated with INI (reference); INNTR associated with INTR; or any drug associated with PIs and the time of current ART. Finally, the use of the older muscle-related drugs tested, such as zidovudine, stavudine, and ritonavir. The multiple models considered the variable was significant when the p-value was ≤ 0.05.

All statistical analyses were performed with JAMOVI® version 2.2.5 Solid Version for macOS. The Software G*Power estimated the sample power *a posteriori*.

Results

The total sample included 70 participants (n = 35 PLWH; n = 35 PNLWH), being 28 men and 7 women for each group. **Table 1** depicts the main characteristics of the sample according to the HIV status. Age, ethnicity, BMI, smoking and drinking habits, schooling level, income, and presence of chronic diseases (i.e., HBP, dyslipidemia, and gastrointestinal disease) did not differ between groups.

Muscle strength and muscle quality

Firstly, HGS (MD = 6.686; p = 0.005) and HGS:ApLM (MD = 0.393; p = 0.005) were higher in control group than in PLWH group.

Table 2 depicts sarcopenia and dynapenia frequencies concerning EWGSOP and SDOC criteria. According to EWGSOP, seven (20%; p = 0.024), three (17.1%; p = 0.046), and seven (20%; p = 0.172) subjects of PLWH group were classified as having dynapenia, dynapenic obesity, and dynapenic abdominal obesity, respectively. When SDOC criteria was applied, twenty-one (60%; p = 0.004), five (14.3; p = 0.020), and two (5.7%; p = 0.151) subjects of PLWH group were classified as having dynapenia, dynapenic obesity, and dynapenic abdominal obesity, respectively.

The regression model 2 (adjusted) having HGS as dependent variable is presented in **Table 3**. This model explained 64% ($R^2 = 0.648$) of HGS ($F = 9.71_{(58,11)}$; $p < 0.001$). High FM: LBM ratio is the factor with higher association with HGS ß = - 15.476; p = 0.007) followed by living with HIV (ß = -7.966; p < 0.001), sex (ß = -7.025; p = 0.019), and age (ß = -0.243; p = 0.038). On the other hand, the ApLMI was the only factor significantly associated with GS (ß = 2.721; p <0.001). Moreover, we conducted a linear

regression model having HGS as dependent variable only in PLWH. This model is presented in **Table 4** and explained 59% (R^2 = 0.589) of HGS (F = $4.65_{(26,8)}$; p = 0.001). High FM: LBM ratio is the factor with higher association with HGS (ß = - 28.371; p < 0.001) followed by ritonavir previous use (ß = - 6.143; p = 0.047).

The sample power and size were estimated a posteriori for HGS and ApLMI. For HGS, considering effect size (0,63), alpha error of 5% and the number of independent variables (n= 9) for multiple models, and sample size (n= 70) the estimated sample power was 0,99.

Body composition and anthropometry

Table 2 depicts body composition- and anthropometry-related parameters. PNLWH presented higher legs FM (MD = 1.78; p = 0.002), ApFM (MD = 2.02; p = 0.011), calf (MD =1.17; p = 0.036) and hip circumference (MD = 3.46; p = 0.036) than PLWH. In contrast, trunk:ApFM (MD = -0.271; p = 0.018), waist-to-hip ratio (MD = -0.043; p = 0.024) were higher in PLWH. Moreover, ApLM (MD = 0.924; p = 0.469), ApLMI (MD = -0.149; p = 0.641), ApLM z-score (MD = 0.206; p = 0.985), and $ApLMI_{FMI}$ (MD = -0.317; p = 0.367) were not different between groups. Concerning $ApLMI_{FMI}$ cutoff below - 1 SD, it was observed that sixteen (45.7%; p = 0.044) P LWH are defined as low $ApLM_{FMI}$.

Table 5 presents the regression model for ApLMI. This model explained 56% (R^2 = 0.565) of ApLMI (F = $6.84_{(58,11)}$; p< 0.001). Being women (ß = -1.212; p = 0.040) was negatively associated with ApLMI. However, FMI (ß = 0.189; p <0.001) and HGS (ß = 0.064; p <0.001) were positively associated with ApLMI. The other independent factors were not significantly associated with ApLMI. **Table 6** presents the regression model for ApLMI considering only PLWH. This model explained 38% (R^2 = 0.38) of ApLMI (F = $1.42_{(23,10)}$; p = 0.234). Only FMI (ß = 0.009; p = 0.009) was associated with ApLMI.

For ApLMI, considering effect size (0,09), alpha error of 5%, the number of independent variables (n= 10) for multiple model, and sample size (n= 70) the estimated sample power was 0,29.

Table 7 presents the ART-related factors. HIV and ART duration was 19 (4 - 31) and 12 (2 - 28) years, respectively. The current ART duration is 4.25 (0.16 - 13) years. The most adopted ART scheme is 2NRTI + INSTIs (51.4%), followed by 2NRTI + NNRTI (20%) and PI associated with NRTI, NNRTI, or INSTIs (28.6%). The most used

drugs were tenofovir (NRTI) plus lamivudine (NRTI) and dolutegravir (INSTIs). Considering NNRTI and PI, the most used drugs were efavirenz and ritonavir, respectively. Concerning earlier generation ART, the most used drugs were zidovudine (AZT) by 14 participants (41.2 %), stavudine (d4T) by five participants (14.7 %), and ritonavir by 13 participants (37.1%) PLWH.

ART-related factors and sarcopenia-related parameters

Table 8 presents univariate regression models investigating the association between ART-related factors and FMI and FM: LBM ratio with the ART use. We verified that previous use of AZT was associated with higher FMI (ß = 2.71; p = 0.038) and FM: LBM ratio (ß = 0.146; p = 0.037).

Discussion

We aimed to evaluate sarcopenia components and sarcopenia-associated factors in PLWH and PNLWH. Our main findings are that considering the EWGSOP cutoff, no person was considered sarcopenic. When applied SDOC cutoff, only one person of PNLWH was defined as sarcopenic. Moreover, considering only lower muscle strength (dynapenia), the EWGSOP cutoff identified one and seven PNLWH and PLWH, respectively. SDOC cutoff identified nine and twenty-one PNLWH and PLWH with dynapenia, respectively. Still, only in PLWH was it possible to identify dynapenic obesity, being 3 and 5 by EWGSOP and SDOC cutoff, respectively.

PLWH presented lower muscle strength (by HGS) and quality (by MQI_{total}) than PNLWH. Moreover, although absolute values of $ApLMI_{FMI}$ were not different between groups, PLWH better met the criteria for low $ApLMI_{FMI}$ (< 1 SD). Regression analyses revealed that FM: LBM ratio, living with HIV, sex, and age were independently associated with lower muscle strength. In contrast, ApLMI was positively associated with muscle strength. Regarding only PLWH, FM: LBM ratio and ritonavir were associated with lower muscle strength. In contrast to our hypothesis, PLWH and FMI were positively associated with ApLMI.

Our results are innovative, especially because previous studies did not verify potential factors related to muscle strength and mass. Is now that, until now, were no available sarcopenia-related cutoffs for PLWH. Thus, we assumed that the criteria validated for aged people without the HIV population would be adopted for PLWH,

particularly considering the anticipated aging hypothesis (driven by low-grade systemic inflammation) [14, 49]. For instance, we adopt SDOC criteria because they include PLWH in the reference sample and are more permissive (especially to men) than EWGSOP2.

Most studies published with PLWH defined sarcopenia only by low ApLMI, considering Baumgartner et al. [45] criteria (< 7.26 kg/m^2) [50-53]. Still, most studies that measured muscle strength only described the mean, median, or lower muscle mass classification without associated factors analysis [54-57]. This may be explained because, until 2019, several studies exclusively used lower ApLMI to define sarcopenia. Thus, we suppose that our data expand the likelihood of sarcopenia-related factors comprehension, especially dynapenia, the most critical component [35, 58].

Muscle strength analysis by HGS is the main method used in dynapenia and sarcopenia definition. Despite discussions concerning HGS to define lower muscle function [59], Oliveira et al. [44] observed that HGS was positively correlated with isokinetic (r = 0.71) and isometric (r = 0.74) peak torque in PLWH. In this report, we applied both EWGSOP (< 27 kg for men and <16 kg for women) and SDOC (< 35.5 kg for men and < 20 kg for women) cutoffs for HGS. The recent SDOC sarcopenia definition included studies that evaluated PLWH [34] and their cutoffs were associated with adverse outcomes, such as mobility limitations and mortality in older men and women [27].

A previous study by Erlandson et al. [44] compared the muscle strength of PLWH and PNLWH and applied both EWGSOP and SDOC cutoffs. Erlandsons' sample was older than ours and comprised men (n = 200; PLWH 59 ± 5 vs. n = 198; PNLWH 60 ± 5 years old) and women (n = 162; PLWH 50 ± 5 vs. n = 85; PNLWH 49 ± 6 years old). Not agreeing with our results, they found no statistical difference between HIV status for absolute values of muscle strength in men (PLWH 36.2 ± 8.5 vs. PNLWH 36.4 ± 7.7) and women (PLWH 27.4 ± 7.8 vs. PNLWH 28.3 ± 5.7). However, similarly to our data, SDOC cutoff generated a higher prevalence of dynapenia than EWGSOP cutoff.

We found that FM: LBM ratio was the most HGS harmful factor. Nevertheless, we observed lower HGS: ApLM ratio in PLWH than in PNLWH, a muscle quality indicator.

Higher amounts of fat mass predict lower muscle quality [60, 61] and immune activation accompanied by LGSI was associated with poor muscle quality in PLWH [26]. WAT contributes to LGSI by several mechanisms [62-66]. For example, PLWHs' WAT

is affected by HIV accessory proteins (i. e., tat, nef, vpr, and vpu) [15]. These proteins induce reactive oxygen species release by mitochondria and damage-associated molecular patterns accumulation [15]. Both could trigger NRLP3 inflammasome activation and increase cytokine production [67]. Still, dysregulated WAT augments bloodstream free-fat acids and their uptake by SkM may lead to lipotoxicity, insulin and anabolic resistance [68]. Previous PLWH studies showed lower SkM density due to higher fact ectopic accumulation [26, 69-72].

Moreover, both WAT and SkM exhibit TLR-4 [73-76]. Living with HIV is associated with poor gut microbiota composition, higher intestinal permeability, and an inflammatory profile. The leaky gut increases LPS translocation that binds to TLR-4 and triggers inflammatory pathways in WAT and SkM. In chronic and dysregulated immune activation conditions, inflammatory cytokines could reach SkM, increasing muscle protein breakdown and decreasing satellite cell proliferation and differentiation [16, 17, 19, 25, 77-80].

ApLMI was not different between PLWH and PNLWH. And living with HIV was positively associated with ApLMI. Our findings corroborate previous studies [81]. Lower muscle function represented by HGS is not accompanied by lower muscle mass, reinforcing that dynapenia appears to be a better predictor of poor outcomes [82], especially in PLWH [35, 58].

Regarding ART, ritonavir's previous utilization was associated with lower muscle strength. In pre-clinical studies, Lopinavir/Ritonavir impairs physical strength [83], and switching Lopinavir/ritonavir to Atazanavir/ritonavir was associated with a better metabolic profile. For example, Stanley et al. [84] verify that this improves muscle glucose uptake, a hallmark of insulin resistance and muscle quality. Besides, previous AZT utilization was positively associated with FMI and FM: LBM ratio. AZT is a thymidine analog and the first drug approved to treat HIV, in 1987. Despite positive effects on viral load, AZT was associated to several detrimental effects [85-87]. Previous studies showed that individuals who received thymidine analog NRTIs as part of older ART schemes present persistent fat alterations several years after discontinuation [88, 89], which was confirmed, at least in part, with our data. ART-related adverse effects correspond to WAT dysregulation and LGSI. Up to 70% of PLWH receiving ART have increased abdominal fat, which is now the most common type of fat alteration in PLWH [90, 91]. Therefore, although AZT was not directly linked to muscle-associated factors, it could lead to poor muscle quality by WAT mechanisms.

Our study presented some limitations, such as (i) sample size; thus, especially by regression analysis, associations must be interpreted with caution; (ii) the number of men is higher than women; (iii) with a cross-sectional study, it is not possible to infer causality; (iv) the origin of the volunteers; therefore, PLWH may present a lower quality of life by stigma and other PLWH-related problems compared to PNLWH. This factor is unlikely to be controlled for in multiple models by inserting educational level or income since it is complex to measure the stigma and the real disadvantage of social problems that PLWH faces. (iv) The sample power and size were estimated *a posteriori*.

In conclusion, PLWH have lower muscle strength and muscle quality than PNLWH. Living with HIV was the main factor associated with low grip strength, followed by arm's FM. ApLMI and $ApLMI_{FMI}$ did not differ between groups. Earlier use of AZT was associated with higher FMI and FM: LBM ratio, suggesting that those who used AZT exhibit WAT-related changes even after its discontinuation. Further studies are needed to confirm our findings, especially with larger samples.

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Tables

Table 1. Sample characteristic of PLWH and PNLWH, São Paulo, Brazil, 2022			
Parameters	Control group (n = 35)	PLWH (n = 35)	p-value
	Mean ± SD or Median, minimum, and maximum		
Age (years)[a]	48 (30 – 55)	47 (28 – 55)	0.972
Ethnicity			0.314
White [n (%)]	25 (71.4)	21 (60.0)	
Non-white [n (%)]	10 (28.6)	14 (40.0)	
BMI (kg/h^2)[a]	26.5 (18 - 40.3)	27.2 (19.8 - 39.6)	0.664
BMI categories			0.438
Underweight [n (%)]	1 (2.9)	0 (0)	
Normal weight [n (%)]	9 (25.7)	10 (28.6)	
Overweight [n (%)]	17 (48.6)	18 (51.4)	
Obesity [n (%)]	8 (22.9)	7 (20)	
Total cholesterol (mg/dL)[a]	158 (126 – 246)	177 (126 – 299)	0.071
LDL-c (mg/dL)	98.7±32.7	112±25.0	0.086
HDL-c (mg/dL)[a]	41 (26 – 68)	40.5 (22 – 90)	0.539
Triacylglycerol (mg/dL)[a]	106 (37 – 219)	149 (45 – 368)	**0.019**
VLDL-c (mg/dL)	22.9 ± 1.4	26.5 ± 8.47	0.102
Glucose (mg/dL)[a]	88 (72 – 109)	93 (73 – 157)	0.165
Hypertension [n (%)]	8 (22.9)	8 (22.9)	1.000
Dyslipidemia [n (%)]	10 (28.6)	15 (42.9)	0.212
Diabetes [n (%)]	0 (0.0)	4 (11.4)	**0.039**
Gastrointestinal disease [n (%)]	6 (17.1)	8 (22.9)	0.550
Smoke [n (%)]	6 (17.1)	6 (17.1)	1.000
Drink alcohol weekly [n (%)]	30 (85.7)	27 (77.1)	0.356
Schooling level [n (%)]			
Basic education	1 (2.9)	3 (8.6)	0.176
High school	6 (17.1)	11 (31.4)	
Under-graduation or post-graduation	28 (80.0)	21 (60.0)	
Income [n (%)]			
< 1 to 3 BMW	9 (25.7)	18 (51.4)	0.075
4 to 9 BMW	16 (45.7	9 (25.7)	
10 or more BMW	10 (28.6)	8 (22.9)	

Legend: Data are presented in mean and standard deviation for parametric variables and median, minimum, and maximum for non-parametric variables. BMI – body mass index; LDL-c - Low density lipoprotein – cholesterol; HDL-c High density lipoprotein – cholesterol; VLDL-c - Low density lipoprotein – cholesterol; Income (< 213,59$ Brazilian Minimum Wage [BMW] is a reference). a - data is non-parametric and was described in the median, minimum maximum. The student t-test, Mann-Whitney U test, and chi-square test were performed on parametric, non-parametric, and categorical variables. **Bold** represents p-value ≤ 0.05. All tests were performed with JAMOVI® version 2.2.5 Solid Version for macOS.

Table 2. Sarcopenia- and Dynapenia-related parameters of PLWH and PNLWH, São Paulo, Brazil, 2022.			
Parameters	Control group (n = 35)	PLWH (n = 35)	p-value
	Mean ± SD or Median, minimum, and maximum		
LBM (kg)	53.7 ± 11.5	51.8 ± 6.91	0.399
ApLM (kg)	25.5 ± 6.35	24.5 ± 4.01	0.469
ApLMI (kg/h^2)	8.30 ± 1.61	8.45 ± 0.96	0.641
Z score ApLM[a]	-0.615 (-2.17 to 1.93)	-0.641 (-1.50 to 2.12)	0.985
EWGSOP Lower ApLMI [n (%)]	2 (5.7)	0 (0)	0.151
SDOC Lower ApLMI [n (%)]	3 (8.6)	0 (0)	0.077
$ApLM_{FMI}$[a]	-0.580 (-5.74 to 2.36)	-0.340 (-3.01 to 4.23)	0.643
Lower $ApLM_{FMI}$ [n (%)]	8 (22.9)	16 (45.7)	**0.044**
Total FM (kg)[a]	25.8 (9.48 – 53)	22.3 (7.75 – 54.2)	0.332
FM (%)	32.4 ± 6.66	31.1 ± 8.72	0.470
Arms' FM[a]	2.57 (1.24 – 4.71)	2.25 (0.93 – 6.33)	0.202
Legs'FM[a]	7.92 (3.49 – 18.2)	5.75 (2.71 – 17.3)	**0.002**
ApFM (kg)[a]	10.6 (4.73 – 21.5)	8.29 (3.78 – 23.0)	**0.011**
Trunk FM (kg)	14.6 ± 6.01	14.4 ± 6.03	0.877
Trunk:ApFM (kg/kg)	1.42 ± 0.42	1.69 ± 0.51	**0.018**
FM:LBM ratio[a]	0.476 (0.195 – 0.854)	0.455 (0.164 – 1.08)	0.356
FMI (kg/h^2)[a]	8.59 (2.82 – 17.4)	7.95 (2.68 – 19.8)	0.545
Z score FMI[a]	-0.133 (-1.85 to 3.83)	-0.184 (-1.31 to 2.16)	0.833
Absolute HGS (kg)	37.8 ± 10.6	31.1 ± 8.67	**0.005**
EWGSOP Sarcopenia [n (%)]	0 (0)	0 (0)	1.000
SDOC Sarcopenia [n (%)]	1 (2.86)	0 (0)	0.314
EWGSOP Dynapenia [n (%)]	1 (2.86)	7 (20)	**0.024**
SDOC Dynapenia [n (%)]	9 (25.7)	21 (60)	**0.004**
EWGSOP Dynapenic obesity [n (%)]	0 (0)	3 (8.6)	0.077
SDOC Dynapenic obesity [n (%)]	0 (0)	5 (14.3)	**0.020**
EWGSOP Dynapenic abdominal obesity [n (%)]	3 (8.6)	7 (20)	0.172
SDOC Dynapenic abdominal obesity [n (%)]	0 (0)	2 (5.7)	0.151
MQI_{total} (kg/kg)	2.82 ± 0.53	2.42 ± 0.60	**0.005**
Gait speed (s)[a]	3.66 (2.82 – 4.73)	3.62 (2.53 – 5.48)	0.906
Calf circumference (cm)	39.1 ± 3.88	37.7 ± 3.30	**0.036**
Waist circumference (cm)	95.3 ± 13.0	96.3 ± 12.0	0.726
Hip Circumference (cm)[a]	101 (90.1 – 127)	98.6 (85.7 – 125)	**0.036**
Waist-hip ratio (cm/cm)	0.91 ± 0.08	0.95 ± 0.07	**0.024**

Legend: Data are presented in mean and standard deviation for parametric variables and median, minimum, and maximum for non-parametric variables. LBM – Lean body mass; FM – Fat mass; ApFM – Appendicular fat mass; ApLMI – Appendicular lean mass Index; FMI – Fat mass index; HGS – Handgrip strength ApLM - Appendicular lean mass; a - data is non-parametric and was described in the median, minimum maximum. The student t-test, Mann-Whitney U test, and chi-square test were performed on parametric, non-parametric, and categorical variables. **Bold** represents p-value ≤ 0.05. All tests were performed with JAMOVI® version 2.2.5 Solid Version for macOS.

Table 3. Linear regression models with Hand Grip Strength as dependent variable, including the whole sample. São Paulo, Brazil, 2022.

	Crude model			Model 1[a]			Model 2[b]		
Variable	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value
Living with HIV	-6.69	-11.3 to -2.06	**0.005**	-7.863	-11.136 to -4.590	**<0.001**	-7.966	-11.319 to -4.612	**<0.001**
Age (years)	-0.329	-0.639 to -0.01	**0.037**	-0.246	-0.466 to -0.026	**0.029**	-0.243	-0.473 to -0.014	**0.038**
Sex (men is the reference)	-14.1	-19.2 to -9.00	**<0.001**	-6.335	-12.025 to -0.644	**0.030**	-7.025	-12.861 to -1.190	**0.019**
ApFM (kg)*	-0.483	-1.10 to 0.139	0.126						
FMI (kg/h^2)*	-0.781	-1.49 to -0.00	**0.031**						
Trunk:ApFM (kg/kg)	2.11	-2.95 to 7.17	0.408						
FM:LBM ratio (kg/kg)	-25.1	-37.5 to -12.7	**<0.001**	-16.801	-27.672 to - 5.930	0.003	-15.476	-26.614 to - 4.339	**0.007**
LBM (kg)*	0.676	0.471 to 0.880	**<0.001**						
ApLMI (kg/h^2)	3.88	2.26 to 5.49	**<0.001**	2.855	1.411 to 4.299	**<0.001**	2.721	1.249 to 4.194	**<0.001**

Legend: Data are presented in mean and 95% confidence intervals. LBM – Lean body mass; ApLMI – Appendicular lean mass Index; ApFM – Appendicular fat mass; FMI – Fat mass index. We conducted linear, univariate, and multivariate regressions, assuming that the HGS was normally distributed with Shapiro-Wilk's test (p= 0.515). The crude model indicates univariate regression; a = in multivariable model 1 we insert all variables whose p-value is ≤ 0.20 plus variables that by biology plausibility affect the outcome (age and sex); b = model 2 is model 1 adjusted by alcohol intake, living with diabetes mellitus, schooling level, and income. * Variables with low tolerance levels (< 0.8) indicated multicollinearity and were not inserted in the multiple or adjusted regression model. In these cases, the variable with the highest beta was inserted into the model. Bold represents p-value ≤ 0.05. All analyzes were performed with JAMOVI® version 2.2.5 Solid Version for mac.

Table 4. Linear regression models with Hand Grip Strength as dependent variable, including only PLWH. São Paulo, Brazil, 2022.

	Crude model			Model 1*			Model 2			Model 3*		
Variable	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value
Age (years)	-0.187	-0.573 to -0.200	0.333	-0.148	-0.463 to 0.167	0.344	-0.244	-0.522 to 0.073	0.134	-0.208	-0.545 to 0.127	0.213
Sex (men is the reference)	-10.5	-17.1 to -3.95	**0.003**	-0.731	-9.226 to 7.763	0.861	-2.584	-11.279 – 6.111	0.545	1.525	-7.005 to 10.056	0.716
FM:LBM ratio (kg/kg)	-27.8	-39.1 to -16.5	**<0.001**	-26.086	-41.579 to -10.593	**0.002**	-24.940	-40.366 to -9.513	**0.003**	**-28.371**	**-43.477 to -13.266**	**<0.001**
ApLMI (kg/h^2)	2.21	-0.866 to 5.29	0.153	1.973	-0.617 to 4.563	0.130	0.880	-1.604 to 3.363	0.472	1.290	-1.276 to 3.857	0.311
2 NRTI plus 1 INSTIs (reference)	1.00											
2NRTI plus 1 NNRTI	-1.94	-9.80 to 5.91	0.618	-0.052	-6.600 to 6.496	0.987	2.013	-4.179 to 8.204	0.509	1.679	-5.157 to 8.515	0.618
Protease inhibitor ART regimens	-4.94	-11.90 to 2.01	0.157	-1.014	-6.840 to 4.810	0.724	-4.128	-9.983 to 1.725	0.159	-3.556	-9.989 to 2.875	0.266
Previous use of AZT	-3.19	-9.12 to 2.75	0.282				4.061	-1.286 to 9.407	0.130			
Previous use of d4T	-3.50	-11.8 to 4.80	0.397				-6.266	-13.090 to 0.558	0.070			
Previous use of ritonavir	-3.57	-9.70 to 2.57	0.245				-5.885	-11.286 to -0.484	**0.034**	-6.143	-12.213 to -0.074	**0.047**

Legend: Data are presented in mean and 95% confidence intervals. LBM – Lean body mass; ApLMI – Appendicular lean mass Index; ApFM – Appendicular fat mass; FMI – Fat mass index. NRTI – Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTI – Non-nucleoside Reverse Transcriptase Inhibitors; INSTIs - Integrase strand transfer inhibitors; PI – Protease inhibitors. We conducted linear, univariate, and multivariate regressions, assuming that the HGS was normally distributed with Shapiro-Wilk's test (p= 0.515). The crude model indicates univariate regression; in multivariable model 1, we insert all variables whose p-value is ≤ 0.20 plus variables that by biology plausibility affect the outcome (age and sex). In model 2, we insert zidovudine (AZT), stavudine (d4T), and previous ritonavir utilization, and in model 3, we maintain ritonavir and adjust it by HIV diagnosis time (in years). All analyzes were performed with JAMOVI® version 2.2.5 Solid Version for mac.

Table 5. Linear regression models with ApLMI as dependent variable, including whole sample. São Paulo, Brazil, 2022

	Crude model			Model 1a			Model 2b		
Variable	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value
Living with HIV	0.149	-0.485 to 0.783	0.641	0.663	0.178 to 1.148	**0.008**	0.584	0.028 to 1.139	**0.040**
Age (years)	-0.00	-0.05 to 0.03	0.676	0.009	-0.020 to 0.039	0.533	0.00	-0.026 to 0.040	0.675
Sex (men is the reference)	-1.51	-2.22 to -0.813	**<0.001**	-1.112	-1.828 to -0.395	**0.003**	-1.212	-2.024 to -0.400	**0.004**
FMI (kg/m^2)	0.090	-0.001 to 0.183	0.054	0.193	0.122 to 0.263	**<0.001**	0.189	0.115 to 0.264	**<0.001**
HGS (kg)	0.065	0.037 to 0.092	**<0.001**	0.067	0.036 to 0.098	**<0.001**	0.064	0.030 to 0.097	**<0.001**

Legend: Data are presented in mean and 95% confidence intervals. ApLMI – Appendicular lean mass Index; FMI – Fat mass index; HGS – Handgrip strength. We conducted linear, univariate, and multivariate regressions, assuming that the ApLMI was normally distributed with Shapiro-Wilk's test (p= 0.460). The crude model indicates univariate regression; a = in multivariable model 1, we insert all variables whose p-value is ≤ 0.20 plus variables that by biology plausibility affect muscle mass (age and sex) and living with HIV (the most important question of this study); b = model 2 was adjusted by alcohol intake, smoking habits, income, schooling level, and living with DM. Variables with low tolerance levels (< 0.8) indicated multicollinearity and were not inserted in the multiple or adjusted regression model. Bold represents p-value ≤ 0.05. All analyzes were performed with JAMOVI® version 2.2.5 Solid Version for mac.

Table 6. Linear regression models with ApLMI as dependent variable, including only PLWH. São Paulo, Brazil, 2022

	Crude model			Model 1			Model 2		
Variable	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value
Age	-0.001	-0.045 to 0.042	0.939	-0.007	-0.053 to 0.037	0.728	0.004	-0.047 to 0.057	0.853
Sex (men is the reference)	-0.671	-1.480 to 0.138	0.101	-0.533	-1.486 to 0.419	0.262	-1.188	-2.455 to 0.078	0.065
FMI (kg/m^2)	0.038	-0.005 to 0.128	0.388				0.190	0.052 to 0.327	0.009
HGS (kg)	0.027	-0.010 to 0.065	0.153	0.008	-0.038 to 0.055	0.709	0.041	-0.021 to 0.103	0.186
2 NRTI plus 1 INSTIs (reference)									
2NRTI plus 1 NNRTI	0.075	-0.826 to 0.977	0.866				-0.180	-1.229 to 0.867	0.724
Protease inhibitor ART regimens	-0.139	-0.938 to 0.659	0.724				-0.119	-1.086 to 0.848	0.801
Previous use of AZT	-0.153	-0.851 to 0.545	0.658				-0.309	-1.183 to 0.564	0.471
Previous use of d4T	0.133	-0.839 to 1.100	0.782				-0.034	-1.209 to 1.141	0.952
Previous use of ritonavir	-0.514	-1.190 to 0.160	0.131	-0.474	-1.198 to 0.250	0.192	0.077	-0.874 to 1.029	0.868

Legend: Data are presented in mean and 95% confidence intervals. ApLMI – Appendicular lean mass Index; FMI – Fat mass index; HGS – Handgrip strength. NRTI – Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTI – Non-nucleoside Reverse Transcriptase Inhibitors; INSTIs - Integrase strand transfer inhibitors; PI – Protease inhibitors. We conducted linear, univariate, and multivariate regressions, assuming that the ApLMI was normally distributed with Shapiro-Wilk's test (p= 0.460). The crude model indicates univariate regression; in multivariable model 1, we insert all variables whose p-value is ≤ 0.20 plus variables that by biology plausibility affect muscle mass (age); Model 2 was adjusted by current ART, previous utilization of stavudine (d4T), zidovudine (AZT) and data of HIV diagnosis. Variables with low tolerance levels (< 0.8) indicated multicollinearity and were not inserted in the multiple or adjusted regression model. All analyzes were performed with JAMOVI® version 2.2.5 Solid Version for mac.

Table 7. ART-related parameters in PLWH (n = 35), São Paulo, 2022.	
ART-related factors	Mean, or Median, minimum, and maximum
Indetectable viral load [n (%)]	35 (100)
Nadir CD4+ T cells/mm^3	375 (10 – 1227)
HIV duration (years)	19 (4 – 31)
ART duration (years)	12 (2 – 28)
Current ART duration (years)	4.25 (0.16 – 13)
2NRTI + INSTIs [n (%)]	18 (51.4)
2NRTI + NNRTI [n (%)]	7 (20)
PI-associated [n (%)]	10 (28.6)
Zidovudine [n (%)]	14 (41.2)
Stavudine [n (%)]	5 (14.7)
Ritonavir [n (%)]	13 (37.1)
Legend: CD4 – Cluster of differentiation; NRTI – Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTI – Non-nucleoside Reverse Transcriptase Inhibitors; INSTIs - Integrase strand transfer inhibitors; PI – Protease inhibitors	

Table 8. Simple models of linear regression models for association between ART-related factors and HGS, ApLMI, FMI and Fat:lean mass ratio of PLWH, São Paulo, Brazil, 2022.

	FMI (kg/h^2)			FM:LBM ratio		
	Univariate			Univariate		
Variable	Beta	(95% CI)	p-value	Beta	(95% CI)	p-value
HIV diagnosis (years)	0.060	-0.098 to 0.216	0.429	0.002	-0.006 to 0.010	0.584
Nadir CD4+ T cells/mm3	-0.003	-0.006 to -6.24e5	0.069	-1.95e-4	-3.46e-4 to -3.38e-6	0.068
ART treatment (years)	0.091	-0.058 to 0.251	0.224	0.003	-0.004 to 0.012	0.370
Duration of the current ART regimen (years)	-0.088	-0.522 to 0.396	0.680	-4.43e-4	-0.024 to 0.026	0.970
2 NRTI plus 1 INSTIs (reference)	1.00			1.00		
2NRTI plus 1 NNRTI	1.14	-1.842 to 5.03	0.500	0.058	-0.107 to 0.273	0.534
Protease inhibitor ART regimens	2.27	-0.655 to 5.850	0.166	0.105	-0.054 to 0.299	0.233
Previous use of AZT	2.71	0.154 to 5.260	**0.038**	0.146	0.009 to 0.284	**0.037**
Previous use of d4T	0.333	-2.860 to 5.180	0.864	0.011	-0.159 to 0.266	0.911
Previous use of ritonavir	0.727	-1.860 to 3.670	0.599	0.016	-0.123 to 0.173	0.824

Legend: Data are presented in mean and 95% confidence intervals. NRTI – Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTI – Non-nucleoside Reverse Transcriptase Inhibitors; INSTIs - Integrase strand transfer inhibitors; PI – Protease inhibitors. For all variables we used linear regression. The lower AIC was used to choose the best regression analysis. All tests were performed with JAMOVI® version 2.2.5 Solid Version for macOS

6.4 Artigo 4 – Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in people living with HIV (PLWH): a systematic review

Clinical Nutrition ESPEN

Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in people living with HIV (PLWH): a systematic review

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Abstract:	Background & Aims: Skeletal muscle losses (both quantitative and qualitative) and the consequent risk of sarcopenia are important issues in people living with HIV (PLWH), even when treated with antiretroviral therapies (ART). We aimed to conduct a systematic review (SR) investigating the effects of dietary interventions with proteins, amino acids, and other nitrogenated compounds on the skeletal muscle of PLWH. Methods: We searched the published literature until August 24 th , 2020, including clinical trials predominantly with AIDS-free PLWH treated with ART. Results: From the 82 studies initially selected, 75 were excluded for the following reasons: nutritional interventions different from nitrogenated compounds; non-nutritional interventions; lack of information on body composition; and studies with most participants with AIDS. From the publications included (n = 7), the majority were performed with small and heterogeneous samples. None of the studies included any new-generation ART or pre- or post-exposition drugs. Two studies found benefits of supplementation on muscle mass; one was performed in a very unfavorable socioeconomic setting, and the supplementation was based on food-derived substances. The other study supplemented creatine, and its benefits were found only when combined with physical exercise training and only by one of the methods of body composition analysis (DXA). Conclusions. Our results showed that nutritional interventions with proteins, amino acids, or other nitrogenated compounds could not improve the skeletal muscle mass in PLWH. Further studies are needed, with bigger sample sizes and more precise control of ART schemes.
Opposed Reviewers:	
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Effect of proteins, amino acids, and other nitrogenated supplements on the skeletal muscle mass in people living with HIV (PLWH): a systematic review

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Abstract

Background & Aims: Skeletal muscle losses (both quantitative and qualitative) and the consequent risk of sarcopenia are important issues in people living with HIV (PLWH), even when treated with antiretroviral therapies (ART). We aimed to conduct a systematic review (SR) investigating the effects of dietary interventions with proteins, amino acids, and other nitrogenated compounds on the skeletal muscle of PLWH. ***Methods:*** We searched the published literature until August 24th, 2020, including clinical trials predominantly with AIDS-free PLWH treated with ART. ***Results:*** From the 82 studies initially selected, 75 were excluded for the following reasons: nutritional interventions different from nitrogenated compounds; non-nutritional interventions; lack of information on body composition; and studies with most participants with AIDS. From the publications included (n = 7), the majority were performed with small and heterogeneous samples. None of the studies included any new-generation ART or pre- or post-exposition drugs. Two studies found benefits of supplementation on muscle mass; one was performed in a very unfavorable socioeconomic setting, and the supplementation was based on food-derived substances. The other study supplemented creatine, and its benefits were found only when combined with physical exercise training and only by one of the methods of body composition analysis (DXA). ***Conclusions.*** Our results showed that nutritional interventions with proteins, amino acids, or other nitrogenated compounds could not improve the skeletal muscle mass in PLWH. Further studies are needed, with bigger sample sizes and more precise control of ART schemes.

Systematic Review Registration

PROSPERO registration number CRD42019139981.

Keywords: HIV; skeletal muscle mass; proteins; amino acids; nitrogenated compounds.

Introduction

The human immunodeficiency virus (HIV) is responsible for the *acquired immunodeficiency syndrome* (AIDS). As the main hallmarks, this disease decreases the $CD4^+$ T cells count, opening the odds to opportunistic infections and an inevitable mortality prognostic [1]. The advent of the antiretroviral therapy (ART) profoundly changed the epidemic trajectory of HIV [2], putting the people living with HIV (PLWH) in an ever-close life expectancy to uninfected people [3].

The current ART schemes include different groups of drugs that inhibit stages of HIV replication, namely, nucleoside/nucleotide and non-nucleoside reverse transcriptase inhibitors (NRTI's and NNRTI's, respectively); protease inhibitors (PI's); CCR5 antagonist or entry inhibitors (EI's) and integrase inhibitors (II) [4]. It is frequent the adoption of an ART scheme with one drug boosted by at least another one [4, 5]; these schemes have been capable of improving the immune response, rendering viral load undetectable, and restoring $CD4^+$ T cells. Besides, other recent pharmacological protocols are directed at people at risk of being HIV-infected, used as pre- or post-exposition drugs [5].

Despite the ART benefits to life quality and expectancy, some side effects of drugs, and a persistent HIV residual effect, bring many metabolic disturbances [6]. For instance, it has been shown several body composition changes such as increase in visceral fat [7] and a reduction in skeletal muscle quantity and quality, which increases the risk of developing sarcopenia [8-12].

Sarcopenia is defined as a state of low muscle strength, muscle mass, and functionality, increasing the risk of frailty, disabilities, and mortality [24]; it is frequently associated with aging but can arise from conditions such as HIV infection, which is classified as "secondary sarcopenia" [11]. Recently, a narrative review conducted by our group investigated, besides the prevalence of sarcopenia in PLWH treated with ART, some possible physiological mechanisms involved in the relationship between HIV, ART, and sarcopenia [13].

Regarding the prevalence, we found it very inconclusive due to different methods and cutoff points adopted to diagnose sarcopenia, different duration of HIV infection, beginning of treatment, and age ranges. Overall, our review showed the prevalence of sarcopenia in PLWH, ranging from 5% to about 30%. Concerning the physiological mechanisms, we constructed a rationale based on the side effects of ART and the HIV residual effect, both increasing the development of a state of low-grade systemic inflammation (LGSI) [14]. Below, we will summarize our rationale for LGSI.

Firstly, cell senescence and immunosenescence are processes anticipated in PLWH, as Nasi et al. [15] elegantly described. Cell senescence leads to a reduced capacity to deal with the so-called danger-associated molecular patterns, which activates the inflammasomes. Secondly, the gut is the primary site of HIV infection, which brings derangement of gut microbiota and the barrier function, originating a leaky gut [16]. Under this conditions, bacterial fragments (mainly the lipopolysaccharide, or LPS) translocate to capillaries and bind to pattern recognition receptors in different tissues, including the skeletal muscle [17]. The consequent signaling to these receptors promotes kinases activation, which can phosphorylate the insulin receptor substrate-1 (IRS-1), reducing insulin sensitivity. Also, some experimental models have pointed out the LPS as responsible for directly impairing skeletal muscle protein synthesis, blunting the anabolic response to amino acids [18, 19]. Thirdly, mitochondrial dysfunction occurs among many side-effects of ART, causing body fat redistribution with loss of subcutaneous fat and accumulation of visceral fat [7]; the increased fat in adipocytes becomes a target of immune cells infiltration, activating inflammatory molecules. These molecules, mainly TNF-α, jeopardize the action of insulin from reduced adiponectin and increased resistin expression and secretion [20-22]. Fourthly, in conditions of insulin resistance, muscle protein synthesis is compromised due to reduced amino acid uptake (via system-A amino acids transport) and blunted phosphatidylinositol 3-kinase (PI3K)-mTORC1 signaling pathway. These conditions also increase non-lysosomal protein degradation [23, 24].

Considering LGSI, insulin resistance, and metabolic consequences, it can be plausible to hypothesize anabolic resistance in PLWH. Studies that conceptualized anabolic resistance showed that in conditions such as aging and obesity, the skeletal muscle turns resistant to anabolic stimuli such as diet and physical exercise. The theoretical basis of anabolic resistance considers conditions such as LGSI and increased body fat, which can be comparable to PLWH using ART, as described above [25-27].

Putting together all these issues, we can hypothesize that non-pharmacologic strategies could improve or mitigate the unfavorable changes in skeletal muscle in PLWH [28, 29]. Therefore, dietary interventions could increase muscle protein synthesis or ameliorate muscle protein breakdown.

Research groups and organizations provide dietary guidelines related to HIV and ART's side effects [30]. Despite these guidelines' importance, they are not specific on nutritional strategies to manage muscle-related issues. Also, there is not any guideline discussing the possibility of side effects of the protein supplementation. In turn, several studies have shown that dietary proteins, amino acids, or other compounds such as creatine could increase muscle protein synthesis, improving the muscle mass in conditions different from HIV-infection [28, 31].

Besides our hypothesis of these substances' benefits, it is indispensable to consider that muscle mass and immune function are integrated with nutritional status [32-34]. At different studies' baseline, people with increased nutritional risk can present different results from persons with a stable nutritional status [35]; for instance, body weight stability may reflect deviation to catabolic conditions [36]. Despite the importance of monitoring nutritional status or nutritional risk before and after dietary interventions, little is explored in PLWH; this importance has been widely discussed in other pathological conditions [36].

Therefore, the present systematic review (SR) aimed to investigate the effect of dietary interventions with proteins, amino acids, and other nitrogenated compounds on the skeletal muscle of PLWH.

Methods

Study type

We performed a systematic review of the literature following The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [37] and methodological recommendations of Cochrane Collaboration [38]. The study protocol was registered at PROSPERO (CRD42019139981).

Review question

We adopted the PICOS formulation detailed in **Table 1** [39], from which we created and refined our research question: *Are nutritional interventions with proteins, amino acids, or other nitrogenated compounds able to improve the skeletal muscle mass in PLWH*? In addition to our outcome (skeletal muscle mass), we extracted data regarded baseline nutritional risk of the participants from all the available data described at the publication.

Search strategies

Databases searched were MEDLINE/PubMed, EMBASE, LILACS, SCOPUS, and Web of Science. Moreover, we searched additional literature by a conventional website browser. From MEDLINE/PubMed we seek descriptors indicated by Medical Subject Headings (Mesh) and Boolean operators "OR" and "AND", as following: (((((((HIV) OR (Human Immunodeficiency Virus)) OR (immunodeficiency Virus, Human)) OR (Immunodeficiency Viruses, Human)) OR (Virus, Human Immunodeficiency)) OR (Acquired Immune Deficiency Syndrome Virus)) AND ((((((((((((((Nutrition Therapy) OR (Therapy, Nutrition)) OR (Medical Nutrition Therapy)) OR (Nutrition Therapy, Medical)) OR (Therapy, Medical Nutrition)) OR (Dietary Supplements)) OR (Dietary Supplement)) OR (Supplements, Dietary)) OR (Dietary Supplementations)) OR (Supplementations, Dietary)) OR (Food Supplementations)) OR (Food Supplements)) OR (Food Supplement)) OR (Nutraceuticals)) OR (Diet, Food, and Nutrition))) AND ((((((((((Body Composition) OR (Body Compositions)) OR (Composition, Body)) OR (Compositions, Body)) OR (Muscles)) OR (Muscle)) OR (Muscle Tissue)) OR (Muscle Tissues)) OR (Lean Body Mass))

OR (Fat-Free Mass)) OR (Lean Mass)). Also, from the Google tool, we identified websites of the field (HIV, body composition) using the same keywords. The search was performed up to August 24th, 2020, without any restriction of the previous date.

Eligibility criteria

The studies had to be clinical, interventional, randomized or not, performed in PLWH, without gender or body mass restrictions. Only studies performed with adults were included. The publications should include most of the participants in the use of ART. The interventions had to be with nutritional supplements such as proteins, amino acids, or other nitrogen compounds, with any intervention length, any form of administration, and any dose, with or without a control group. The skeletal muscle mass could be assessed by any validated method [bioelectrical impedance (BIA), dual-energy X-ray absorptiometry (DXA), magnetic resonance image (MRI), computer tomography (CT), total body potassium count (TBK), and anthropometric measures (fat- free mass obtained from predictive formulas or calf circumference)]. The publication languages had to be English, Spanish, or Portuguese. The exclusion criteria were: (i) regarding the study design: studies with non-human or *in vitro* models or literature reviews; (ii) regarding the participants: pregnant women, described presence of AIDS at the time of the experiment (category "C," or III or IV according to WHO, participants with comorbidities associated to muscle loss other than the HIV; (iii) regarding intervention: use of anabolic steroids, myostatin inhibitors, growth hormone; or studies using any other alternative therapy for HIV different from ART.

Procedures for developing the systematic review

Our systematic review was developed according to the following steps:

1st step. Reading the titles and abstracts, excluding the ones not related to the research question and the duplicates. Two authors (MVLSQ and CMM) performed this step and checked by the third author (SMLR); inconsistencies were solved in a consensus meeting.

2nd step. Obtainment of the selected articles in full and reading to identify in detail the inclusion and exclusion criteria. Two authors performed this step independently (MVLSQ and CMM), and the divergences were solved in a consensus meeting with the third author (SMLR).

3rd step. Data extraction of the studies by the first author (MVLSQ), checked by the second author (CMM), and organized in commercially available spreadsheet software. The data extracted were location and time of the study, study aims, study design, sample characteristics, antiretroviral therapy scheme, type of intervention, control group (if any), intervention duration, information about the nutritional risk (referred by the article's authors or inferred by the present SR's authors, from different variables described at the text), physical activity and diet information, side effects of the intervention, methods of analyzing body composition, main results, and summary of the findings.

Quality assessment (risk of bias)

The risks of bias were assessed independently by two researchers (MVLSQ and CMM), and the divergences were solved from a consensus meeting, including the third author (SMLR). We adopted the Cochrane risk of bias tool v.2 and used the software RoB2 [40]. According to these tools, the risk of bias is evaluated considering the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. The overall risk of bias evaluation is subjective and decided among the research team. We decided to define the risk of bias based on the majority of the five items' decisions (high risk, some concerns, or low risk).

Results

Searches

The searches resulted in 1486 publications. After excluding 223 duplicates, 1.263 articles were screened from titles and abstracts. From these readings, 1.180 studies were excluded for not meeting the eligibility criteria, and therefore 82 were selected for a full reading. This step leads to the exclusion of 75 studies. After double-checking our exclusion and inclusion criteria, sixty-eight

studies were excluded. The main reasons for exclusions were: Nutritional interventions different from our research question (n = 20); Studies type different from clinical intervention type (n = 20); Lack of information on body composition analysis (n = 14); Inclusion of most participants with AIDS (n = 9); Lack of nutritional intervention (n = 7); Participants with comorbidities related to muscle mass losses for reasons other than HIV (n = 2); sample with pregnant women (n = 1); use of anabolic drugs in the intervention (n = 1); and non-availability of the publication, even upon request to the authors (n = 1). Therefore, seven studies were included in the subsequent stages of the systematic review [41-47]. **Figure 1** depicts the flow process of studies election.

Insert figure 1.

Risk of bias and quality assessment

Figure 2 shows the individual risk of bias, and the overall risk is shown in **Supplementary Table 1**. Only one study was classified as "low risk" [41], and six studies were classified as "with some concerns" [42-47].

Insert figure 2.

Summary of findings

Tables 2 and **3** depict the data extracted from the studies. Three of them were from North America (United States of America), three were from Europe (two from Switzerland and one from Germany), and one from Asia (India). Four studies were randomized and double-blinded [41, 44-46], and three were randomized and open-label [42, 43, 47]. Overall, the intervention time varied from 8 weeks to 6 months, and the sample sizes ranged from 30 to 68 participants; two publications included only women [43, 47]. Five out of the seven studies evaluated the body composition by bioelectrical impedance (BIA) [41, 42, 44, 45, 47], one study combined DXA and MRI, and one combined DXA, MRI, and TBK [43, 46]. All the studies included patients in the use of ART. However, some publications, generally due to ethical concerns, allowed some participants' entry without using the therapy, provided that some conditions related to symptoms, viral load, or $CD4^+$ T cells were met.

Insert tables 2 and 3.

Pichard et al. [41] performed a randomized, double-blinded study with 64 PLWH. The age range was approximately from 30 to 39 years old. The study aimed to evaluate the effects of a supplement high in casein and enriched with arginine and ω-3 fatty acids (intervention group; n=32) against a control group receiving only casein (n = 32). The mean BMI of the participants at baseline was 21.8 ± 0.4 kg/m^2 in the control group and 22.5 ± 0.5 kg/m^2 in the intervention group. The CD4$^+$ T cells count was 432 ± 45 and 419 ± 48/L in the control and intervention groups, respectively). Therefore, we can consider the nutritional status of the participants as a "mild nutritional risk". The food intake was monitored monthly by 3-day non-consecutive food questionnaires, and the physical activity level was not reported. The study lasted 6-months, and the body composition was analyzed at the experiment's beginning and end. The skeletal muscle was analyzed by BIA, from which the authors estimated the fat-free mass (FFM); muscle strength was not analyzed. The ART schemes were composed of NRTI and NNRTI. At the end of the experiment, the authors did not find any significant differences in body composition. Five participants from the intervention group and four participants from the control group dropped out of the study due to intolerance to the supplements given. The authors did not account for the ART schemes when discussing the results. We attributed the bias classification as "low risk" since all the tool items were described as low risk.

Schwenk et al. [42] conducted a randomized, open-label study of 50 PLWH. The age range was approximately 29 to 49 years old. Two groups were compared, supplementing (intervention group) or not (control group) a soy-based substance; both groups received nutritional counseling to increase their energy intake throughout the experiment. The diet was monitored by 24-h food recalls. The physical activity level was not informed. The sample comprised individuals with a BMI of 19.9 ± 2.1 and 19.6 ± 2.3 kg/m^2; they presented previous weight loss (> 5% total weight loss) and were actively losing weight (> 3% within the last month); the CD4$^+$ T cell count was 180 ± 198 and 160 ± 164 cell/uL, and the viral load was of 4.1 and 4.7 log^{10} copies/mL (all these

parameters in intervention and control groups respectively). We considered the sample as "increased nutritional risk" (due to the active body weight loss and low $CD4^+$ T cell count). The body composition was assessed by BIA; the FFM was estimated using standard equations; muscle strength was not investigated. The study was conducted at the time of the introduction of PI in the ART schemes. The participants were stratified according to the use of PI (continuing treatment without protease inhibitor; continuing treatment with protease inhibitor and new protease inhibitor). The study lasted eight weeks, and the parameters were analyzed at baseline, six and eight weeks. FFM did not change significantly between groups at the end of the study. The participants who started the treatment with PI (newer PI) tended to gain more FFM (although without significant results). The tolerance to the oral supplement was described as better than previous results from the same population. The risk of bias was classified as "some concerns," mainly due to not being a blinded study.

Agin et al. [43], in a randomized, open-label study with 37 female PLWH (age range from 28 to 66 years old), aimed to compare three different interventions; whey protein supplementation (1 g/kg/day; PRO; n = 12) alone; progressive resistance physical training intervention (PRE; n = 12) alone; or a combined intervention (PRO + PRE; n = 13). At baseline, the participants' BMI were 23.4 ± 2.0 kg/m^2, 24.8 ± 2.5 kg/m^2, and 23.0 ± 2.3 kg/m^2 (PRO, PRE, and PRO-PRE interventions, respectively). The $CD4^+$ T cells counts were 215.3 ± 295, 248 ± 176.3, and 335.1 ± 295 cells x 10^6/L in the PRO, PRE, and PRO-PRE groups. The stability of the participants' status allowed us to classify the sample as "mild nutritional risk". Food intake was evaluated from in-depth face-to-face and telephone interviews. The study lasted 20 weeks (6 control and 14 intervention weeks). The evaluations were performed at weeks zero and six of the control period to assure the stability of the variables and then at 14 weeks of intervention. The body composition was analyzed using TBK; the skeletal muscle and body fat were measured by MRI and DXA. The muscle strength was measured by a 1-maximum repetition of seven muscle groups. Regarding the ART scheme, this study was conducted from October 1997 to May 1999, just following the local

availability of highly active antiretroviral therapy (HAART); the main objective of the study was to observe if the introduction of nutritional supplementation and physical exercise could bring additional benefits in body cell mass to HAART. However, the study did not specify the type of drugs used. Seven women did not complete the intervention for non-compliance, six due to family constraints (two from each group), and one death (PRO-PRE group). One patient (PRO-PRE group) referred nausea when consuming the protein supplement, and due to this, she received a half dose at 0.5 g/kg per day for the entire treatment period. Adherence to protein treatment was 96% for PRO and 93% for PRO-PRE groups. As the main result, despite the body weight and body fat increased in the PRO group, there was no change in skeletal muscle by the three methods of investigation. All the seven muscular strength (1-maximum repetition) increased for the exercise groups (PRE and PRO-PRE). There were no additional analyses by HAART because of the reasons described above. The combined PRO-PRE group did not increase these muscle variables. Therefore, the treatment of BCM-wasted female PLWH did not improve skeletal muscle parameters. The blindness of the study was not clearly described; therefore, the risk of bias was classified as "some concerns."

Karsegard et al. [44] performed a randomized, double-blinded study with 46 PLWH. The age range was not informed. The experimental design aimed to investigate the effects of L-ornithine-ketoglutarate (OKG; 10 g/day against the same amount of isonitrogenous placebo. In the intervention and control groups, the authors included subjects with stable BMI and within the normal ranges (20.0 ± 2.4 kg/m^2 and 20.6 ± 3.0 kg/m^2, respectively). However, the inclusion criteria were the presence of involuntary weight loss of 5% to 15% of their usual weight since the beginning of HIV infection. In the intervention and control groups, the CD4$^+$ T cells count was 337.6 ± 172.4 and 310.2 ± 136.4 cells/mL, respectively. The mean plasma albumin was within the normality ranges (43.8 ± 6.0 g/L and 42.6 ± 5.7 g/L for intervention and control groups, respectively). We considered the sample as at "increased nutritional risk", mainly due to the weight loss above 10% by part of the sample. The food intake was monitored from 3-daily food records

applied one week before each evaluation. The authors mentioned the physical activity level to be evaluated by pedometers but did not present these results. The experiment lasted 12 weeks, and the evaluations were performed at baseline and weeks 4, 8, and 12. The body composition was assessed by BIA, from which the authors estimated the FFM; the muscle strength was measured by handgrip strength. The participants were subjected to different ART schemes, including PI, NRTI, NNRTI, and adherence to the ART was not described. Out of 46, thirteen participants were not in ART use (5/22 in the OKG group and 8/24 in the control group); the authors did not conduct any additional analysis by ART schemes. None of the groups increased their FFM or muscle strength at the end of the experiment. Fifty-four percent of the participants in the OKG group referred to gastrointestinal symptoms. The dropout range was high (50% in the experimental group and 25% in the placebo group). Mainly because of this, the bias classification as "some concerns"; even with the adoption of intended to treat analysis.

Sattler et al. [45], conducted a randomized double-blinded study with 59 PLWH, with a median age of 52 years old for women and 41 years old for men; the authors informed neither standard deviation nor range, although they described the proportion of voluntaries above 50 years old (17% in the intervention and 20% in the control group). The experimental design consisted of two groups; the intervention group received a high-protein supplement with 40 g whey protein, 20.5 g carbohydrate, and 4.0 g fat per 280-kcal serving. The control group received an isocaloric control supplement with 0.6 g casein (protein), 60.8 g carbohydrate (high-maltose rice syrup solids), and 4.0 g fat per 280-kcal serving. The two supplements were taken twice daily between meals and intended to increase daily energy intake by 560 kcal. Concerning the baseline nutritional status, the mean values of BMI were within the normality ranges (20.7 ± 2.3 and 21.1 ± 2.8 kg/m^2 in the intervention and control group, respectively). Twenty-one percent of the intervention group and 20% of the control group were classified as low body weight (BMI < 18.5 kg/m^2), however, the authors included in their study only persons with stable weight loss, which was defined as prior unintentional weight loss >3% throughout the HIV-1 infection, but no change in weight >3%

during the last two months. The immune status and viral load were heterogeneous between and within groups; in the intervention group, the distribution of $CD4^+$ T cell <200 cells/mL was 21%; between 200 and 500 cells/mL was 56%, and > 500 cells/mL was 24%.; the respective percentages in the control group were 6%, 63%, and 27%. From this information, we considered the participants as "at increased nutritional risk". The food intake was investigated by 3-d food intake diaries and showed that, at the baseline, the participant's energy and protein intake were above the requirements. The authors did not inform the physical activity level. The experiment lasted 12 weeks, and measures were performed at baseline and the end of the study. The body composition was evaluated by anthropometric measurements and BIA, from which the authors estimated absolute and relative lean body mass (LBM). Muscle strength was not measured. The participants were on different ART schemes. All participants received two to three drugs among PIs, NRTIs, or NNRTIs; the compliance (or adherence) to ART was not mentioned; one participant in the control group was not in the use of ART. The authors did not find any significant difference in the body composition variables at the end of the study. They justified the findings because the participants reduced their self-selected food intake. Also, gastrointestinal symptoms occurred more often in the intervention group compared with the control group. Concerning the risk of bias, we considered the study as "some concerns" because the assessors possibly were not blinded to the study.

In a randomized and double-blind study, Sakkas et al. [46] investigated in 40 PLWH (age range approximately 35 to 54 years old) if a creatine supplementation protocol could have additional benefits on the effects of physical exercise training. Two groups were constituted; one was submitted to supervised resistance physical exercise training (PRT; n = 20). The other group received the PRT plus creatine supplementation (5 days of 20 g loading dose, followed by 4.8 g maintenance dose; n = 20). The BMI mean values at baseline were considered within the normality range (23.7 ± 2.6 and 23.7 ± 2.5 kg/m^2, creatine and placebo groups respectively), and the $CD4^+$ T cell count were 448 ± 310 and 460 ± 278 cells/uL in creatine and control group, respectively.

Therefore, the participants could be considered "mild nutritional risk". The authors did not provide any information about the participants' dietary intake. Regarding ART, the participants used two or three combinations of PI, NTRI, and NNTRI; 11 participants were not in ART use (4 out of 20 in the creatine group and 7 out of 20 in the control group). The study lasted 14-weeks, and the evaluations were performed comparing changes after 2 and 14 weeks. The body composition was analyzed by MRI and by DXA. Muscle strength was measured from isometric maximum contraction force during ankle dorsiflexion by magnetic resonance spectroscopy. Thirty-three participants completed the study. Seven participants withdrew due to hypersensitivity reaction (1 in creatine group), schedule conflicts (2 in creatine group), family issues (1 in the placebo group), and non-adherence, which was considered by missing three consecutive PRT sessions (3 in the placebo group). Regarding side effects, the authors monitored the serum creatine levels biweekly; in case of levels increasing > 1.8 mg/dL or CK > 450 U/L, the supplementation was interrupted for one week. Four subjects faced these increases, but the values returned to normal in all cases, and the experiment continued normally. The LBM improved with PRT, and this improvement was more significant in the creatine group only by DXA analysis; the data provided by the authors did not allow us to calculate the effect size. The MRI analysis did not show significant differences in the thigh muscle cross-sectional area. Strength increased significantly within each treatment group, but there was no significant difference between groups in the magnitude of the increase in creatine and placebo. There was not any analysis regarding ART schemes. Concerning the risk of bias, we classified it as some concerns, mainly because the authors did not conduct an intention to treat analysis.

Nyamathi et al. [47] conducted a pilot, randomized and open-label study with 68 female PLWH from a rural area of India. The age range was 20 to 45 years old. The authors compared two interventions, the first composed of a high protein preparation (with black gram and pigeon peas), combined with education and supportive care (AL); the control group received a standard protein supplement made with chickpeas combined with usual care (UC). The authors did not provide any

information about the participants' regular dietary intake or physical activity level (although the poor social conditions described led to infer the low quality of both lifestyle variables). The average BMI at baseline was 20.0 ± 3.4 and 19.0 ± 2.5 kg/m^2, the CD4$^+$ T cells count were 439.1 ± 217.6 and 447.5 ± 260, in the intervention (AL) and control (UL) groups, respectively. The CD4$^+$ T cells <100 was an exclusionary criterium. Although these parameters allow us to consider the nutritional status as adequate, the social and economic conditions described led us to consider the sample as "at increased nutritional risk". The experiment lasted 6-months, and the evaluations were performed at 3 and 6 months. The body composition was measured by BIA, from which the authors estimated the LBM. Muscle strength was not measured. The type of ART combination was not informed, although being in the ART regimen for at least three months was a criterion for inclusion in the study. The AL group showed, after six months, a significant improvement (time and group interaction) in all the parameters evaluated, including the LBM. The authors also observed that the intervention increased ART adherence; the body composition increased more expressively in those with adherence to ART higher than 66%. To highlight the importance of analyzing the effect of ART on supplementation, we calculated Cohen's effect size for these improvements [48]. The simple comparison between the intervention and control group showed effect sizes of 0,03 to the intervention group and 0,00 to the control group; to the participants with ≥ 66% adherence to ART, the effect size increased to 0,36 to the intervention group and 0,10 to the control group at three months interval. There were no descriptions of any side effects of the supplements given. Despite some items being evaluated as high risk of bias, the local conditions of the study were very typical and did not allow different evaluations. Overall, we classified the risk of bias as "some concerns".

Discussion

This SR investigated the effects of proteins, amino acids, and nitrogen compounds supplementation on skeletal muscle parameters of PLWH. Seven publications were included, from which five did not significantly improve muscle mass parameters, and two did show modest improvements. One study was conducted with a group under critical socio-economic issues,

possibly facilitating the benefits; the second study found improved muscle mass with creatine supplementation, but only when combined with physical exercise training and only from DXA analysis. Among the studies, we found several possible confounders that could explain the absence of intervention effect. The confounders are (i) age range of the voluntaries; (ii) absence of detailing of and sub-analyses according to ART schemes; (iii) different nutritional risk among the participants; (iv) lack of dietary intake and physical activity control; (v) different methods of body composition analysis and; (vi) possibility of different metabolic and physiological responses to the different types of supplements. We will conduct our discussion based on these possible confounders.

Age range

The reduction in muscle mass is one of the components of the sarcopenia. Relevant published studies demonstrate aging as a critical factor in qualitative and quantitative changes in skeletal muscle [49, 50]. We noticed a wide age range in the studies included in our SR, with participants from their twenties to sixties. Thus, sub-analyses by age group would make the results more appropriate for discussing the effects of HIV and ART.

ART schemes

In the introduction of this manuscript, we described possibilities of skeletal muscle issues in PLWH. Briefly, the residual effect of the virus and several side-effects of the different drugs included in ART could create an inflammatory environment that can be, at least in part, similar to the mechanisms related to anabolic resistance. As such, the description and analyses of the ART are essential information to conduct an appropriate analysis of our research question. However, only two studies performed this type of analysis. Nyamati et al. [47] did not consider the type of drug but instead the adherence to ART schemes. They found that an adherence above 66% increased the benefits of the intervention; we calculated the effect sizes of their analyses; although the values increased in the stratified analyses, the effect size was still small. Also, Schwenk et al. [42] considered three conditions related to ART treatment (starting PI, without PI, or continuing

the use of PI). Although without statistical significance, the authors observed higher numerical FFM in the group who changed to the newer PI at baseline. Sakkas et al. [46] although not performed any additional analysis according to the ART scheme, hypothesized that the absence of significance in their results could be due to ART interference; they mentioned the effect of PI on glucose metabolism with consequent reduction of glucose uptake by skeletal muscle.

Despite side effects, the PI are frequently adopted in different ART schemes because of their high efficacy in controlling the viral load. The early generation of PI, namely indinavir and ritonavir, is described to inhibit essential enzymes of energy metabolism and to promote changes in skeletal muscle. Besides, higher intramuscular triacylglycerol (due to mitochondrial dysfunction) can compromise oxidative efficiency, increasing the inflammatory status and insulin resistance [51, 52]. The most recently developed PI, such as tipranavir and darunavir, are proposed to reduce these side effects. However, some publications comparing both generations are not conclusive in this respect. The "newest" PI have shown a tendency for increasing visceral fat, despite improvements in blood lipids profile [53, 54]. Thinking about our research question, an increase in visceral fat is not compatible with an increase in skeletal muscle mass and quality.

Our SR showed a lack of studies with other newer generations ART drugs, for instance, entry inhibitors or integrase inhibitors. Most studies of this SR were published between 1998 to 2013, therefore before the advent of these drugs. Another noteworthy fact from our results is that from the seven studies, two of them [44, 46] included about 30% of the participants who were not in the use of ART, and one study included one participant without ART [45]. Although the inclusions of that voluntaries occurred in combination with favorable conditions related to viral load and $CD4^+$ T cell count, the metabolic effects of ART can make the groups more heterogeneous, difficulting a discussion of the results. Summarizing the ART topic, the heterogeneity and the lack of treatment details are limitations of all the studies included in our SR.

Nutritional risk

The effects of any protein (or nitrogenated compounds) supplementation are closely related to protein-energy malnutrition (PEM) status, as discussed in clinical nutrition settings [35, 55]. An effective indicator of PEM risk is body weight, investigated both statically and dynamically. Even being aware that living with HIV is a common factor in defining the participants as "at nutritional risk", we noticed important information in some studies, mainly the body weight instability and heterogeneous $CD4^+$ T cells count. Weight loss is part of the PEM risk definition [35, 55]; the $CD4^+$ T cells count is essential to immune responses and, consequently, nutritional status stability [56]. As such, we tried to classify the different samples of our SR as "increased nutritional risk" or only "mild nutritional risk". In addition, in one study [47], we opted to classify the participants' nutritional risk as increased because of the unfavorable socioeconomic setting, despite body weight stability.

From our attempt to differentiate the nutritional risk, the studies of Pichard et al. [41], Agin et al. [43], and Sakkas et al. [46] included participants with mild nutritional risk and, therefore, reduced their confounders in the analyses.

Food intake and physical activity as control variables

Food intake is a fundamental component to be controlled to allow the differentiation of the effects of a protein supplement. Despite this, two of the seven studies did not control this variable [46, 47], and the studies that mentioned controlling diet did not perform a quantitative analysis showing the adequacy of nutrients, particularly proteins and energy. The nutrients supplementation is only justified if the diet cannot fulfill the requirements.

In addition to food intake, physical exercise is also an important anabolic stimulus to increase muscle protein synthesis. Both (food intake and physical exercise) stimulate the mTOR signaling pathway [57-59]. In our SR, two studies included physical exercise as part of the intervention [43, 46], and the results showed favorable effects of physical training on muscle mass; only one of these studies showed additional benefits with nutritional supplementation, particularly with creatine [46]; these benefits were significant only when in combination with the physical

exercise training, and only from the DXA analysis. In turn, the study conducted by Agin et al. [43] tested the additional effect of whey protein supplementation on the benefits of physical exercise training but did not find significant effects of the supplement.

Even in non-HIV samples, the effects on the muscle mass of different nitrogenated compounds, together or not with physical exercise, are not yet fully known [60-62]. More studies with PLWH are needed, including the possibility of anabolic resistance in these persons.

Methods of assessing body composition

Excess body fat, the consequent augmented inflammatory status, and oxidative stress, typical changes in PLWH, raise concerns about the methods to investigate body composition. The inflammation is associated with an imbalance in water homeostasis [104]; it can be an issue when using BIA to investigate body composition. This technique requires different equations to estimate body composition, which generally considers constant body water [63, 64]. Therefore, the interpretation of the results can be compromised [65]. Likewise, the DXA imaging method cannot identify body water, and its measurements also assume this content as constant [64]. The differences found in the results of Sakkas et al. [46] according to the method of the investigation confirm, at least in part, these issues. MRI or TBK may probably provide more reliable results, especially in PLWH, but they are expensive techniques that are not affordable for most settings.

Type of Supplements: intact proteins, plant-based proteins, and nitrogenated compounds

Five studies adopted supplements with intact proteins [41-43, 45, 47]. Two studies adopted whey protein [43, 45], one in a high caloric compound [45], and the other used the supplement isolated [43]. Whey protein is a widely used nutritional supplement and has shown promising results, with or without physical exercise, in young and older adults without HIV [66-68]. The two studies conducted with whey protein [43, 45] did not improve muscle mass. A possible explanation for these unexpected results can be an inadequate dosage or the presence of anabolic resistance in PLWH. In turn, Sattler et al. [45] discussed the existence of a threshold of protein intake to justify

the absence of positive results; the authors monitored the food intake and observed that at baseline, the participants consumed protein at RDA two-fold.

Two studies adopted plant-based proteins to their supplementation protocol [42, 47]. Schwenk et al. [42] compared the effect of soy-based protein-energy supplement plus nutritional counseling in PLWH. The energy intake was monitored, and both groups consumed a high-energy diet during the eight weeks of the experiment. They did not find any benefits of the supplementation on muscle mass. In turn, Nyamathi et al. [47] tested the effect of a legume-based high protein supplement plus counseling. They found improvements in muscle mass from the high-protein plant-based supplement. This study assumed a particular feature since it was performed in low economic and social conditions. The benefits from the supplements possibly are more associated with the counseling strategy given than with the supplement *per se*.

Some authors point out that plant-derived proteins intake results in lower post-prandial muscle protein synthesis when compared with animal-based protein. This low protein synthesis is because of differences in the digestion and amino acid absorption kinetics; the amino acid composition can also be considered. A plant-based diet is accompanied by a transition towards more expressive dietary protein intake requirements [69]. A study performed with a non-human model showed that the mTORC1 response following ingestion of high-quality plant-based is dampened compared to whey-protein in mouse skeletal muscle [70].

Finally, three studies adopted other nitrogenated compounds in their supplementation protocol. Sakkas et al. [46] studied the effect of creatine monohydrate and physical exercise training; they used the recommended protocol of an initial loading dose (20 g per day), followed by a maintenance dose (4.8 g). Creatine is a nutritional supplement that enhances short-term energy availability (phosphocreatine-ATP system). The main effect on muscle mass generated by creatine is attributed to improvement in training-mediated anabolic signaling. Creatine could activate anabolic pathways of IGF-1, myogenic factors, and satellite cell differentiation and mitigate the activation of catabolic proteins such as myostatin, MuRF1, atrogin-1, FOXO, and other proteins

related to sarcopenia [71]. The authors observed positive results of the supplement in LBM by DXA, which was not confirmed by MRI [46]. The limitations regarding the methods to investigate body composition discussed above could put in doubt the benefits found by DXA analysis.

Karsegard et al. [44] investigated the ornithine-keto glutarate (OKG) on muscle mass. It is hypothesized that OKG, as a glutamine and glutamate source, could stimulate muscle protein synthesis and decrease muscle protein breakdown. The OKG is also thought to be an energy fuel for the gastrointestinal cells, which would reduce bacterial translocation and, therefore, improve the LGSI [72]. However, the authors did not find significant results [73].

Pichard et al. [41] tested nitrogenous non-protein compounds, adding the amino acid L-arginine and ω-3 fatty acids in a casein-based protein. Although not detailed by the authors, we can infer that the addition of ω-3 could give an anti-inflammatory advantage to the supplement [74]. However, their results did not show any advantage on this combination. A recent review concluded that ω-3 has no positive effects on muscle mass and strength in young and older adults [75]. Arginine can be synthesized endogenously from glutamine, glutamate, and proline; this supplementation increases GH secretion, creatine synthesis, and nitric oxide production [76]. Besides, cell culture studies suggest that arginine could increase MPS by increasing mTOR phosphorylation [77, 78]. However, the effects of arginine on muscle mass and strength are scarce based on clinical studies.

From our results, we did not identify any better supplement to be adopted by PLWH, which could once again raise the possibility of anabolic resistance.

Gastrointestinal effects of supplementation

Four [41, 43-45] out of the seven studies in this SR reported gastrointestinal-side effects, which deserve careful analysis. The reference to diarrhea can be associated with a poor gut environment, which is undesirable, especially in PLWH. It is known that the first body region infected by HIV is the gastrointestinal tract, which drives significant gut environmental changes such as dysbiosis [15, 79, 80]. Gut dysbiosis increases gut permeability, microbial translocation,

and LGSI [16]. This dysregulation also modifies the production of critical microbiota-derived metabolites, worsening metabolic functions [81-83]. Our SR descriptions of side effects were associated with different supplements (whey protein, casein/arginine/ω -3, OKC, and creatine). We cannot guarantee that the type of supplement is the main issue. For instance, Sattler et al. [45] also supplemented whey protein and did not refer to any side effects. Agin et al. [43] solved the gastrointestinal issues by changing the dosage, and Sakkas et al. [46] temporarily interrupted the protocol and restarted one week later without further complications. These aspects must be carefully considered in future studies. Maybe, the association with substances driven to modulate gut microbiota such as pre, pro, or symbiotic should be planned.

In conclusion, studies with protein and other nitrogenous compounds to improve the skeletal muscle in PLWH are still small, heterogeneous, and did not include the new-generation ART. Our findings did not allow any evidence or recommendation. Several factors must be considered in future studies evaluating proteins supplementation in PLWH: (i) a clear description of food intake and physical activity as control variables; (ii) the ART details in the baseline and follow-up, (iii) the nutritional risk of the participants considering mainly unstable variables. Also, the advent of pre- and post- exposition drugs in the prevention of HIV infection demands the comprehension of muscle issues in these non-infected persons.

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Author's Contributions

Contributions to the manuscript: MVLSQ, CMM, and SMLR collaborated with design, writing, and final content, and all authors have read and approved the manuscript.

Conflicts of interest/Competing interests

None of the authors have any conflict of interest to declare.

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Table 1. PICOS criteria for inclusion of studies	
Parameter	Description
Participants	People living with Human Immunodeficiency Virus
Intervention (exposure)	Nutrition therapy and dietary supplements
Comparison	Not applied
Outcome	Lean body mass or Fat-free mass or Muscle mass
Study design	Clinical studies

Table 2. Main features of the studies included in the SR.

Author (year) [ref]	Location and time of the study	Study design	Sample	ART schemes
Pichard et al. (1998) [41]	Switzerland; between August 1995 and January 1996	RDB	55 PLWH Intervention group: n = 27; 36.7 ± 1.6 years old; CD4 (count/mm^3) 419 ± 48; 85.2% men Control group: n = 28; 32.6 ± 1.8 years old; CD4 (count/mm^3) 432 ± 45; 75% men Economic status of participants not reported	Zidovudine (NRTI): n = 7 in intervention group and n = 5 in control group; didanosine (NRTI): n = 4 in intervention group and n = 2 in control group; zidovudine + didanosine: n = 1 intervention group and n = 0 in control group
Schwenk et al. (1999) [42]	Germany; between March 1996 and December 1997	ROL	50 PLWH Intervention group: n = 26; 39.4 ± 9.2 years old; CD4 (µL) 180 ± 198; 100% men Control group: n = 24; 39.5 ± 10.2 years old; CD4 (µL) 160 ± 164; 21; 87.5% men Economic status of participants not reported.	Continuing treatment without PIs: n = 9 in intervention group and n = 15 in control group; Continuing treatment with PIs: n = 7 in intervention group and n = 3 in control group; New PIs study entry: n = 10 in intervention group and n = 7 in control group
Agin et al. (2001) [43]	USA; from October 1997 to May 1999	ROL	30 women PLWH Nutritional Intervention (PRO): n = 10; 38.2 ± 8.6 years old; CD4 (count 10^6/L) = 215.3 ± 295 Exercise Intervention (PRE): n = 10; 41.0 ± 10.2 years old; CD4 (count 10^6/L) = 248.8 ± 176.3 Nutrition plus exercise Intervention (PRE-PRO): n = 10; 43.4 ± 10.6 years old; CD4 (count 10^6/L) = 335.1 ± 295 Economic status of participants not reported	Although the authors commented that the intervention period was made after the availability of antiretroviral therapy, there are no details on what types of drugs and combinations were used
Karsegard et al. (2004) [44]	Switzerland; between 1995 and 1997	RDB	46 PLWH Intervention group: n = 22; 32.4 ± 5.2 years old; CD4 (count/mm^3) 337 ± 172.4; 50% men Placebo group: n = 24; 34.9 ± 5.2 years old; CD4 (count/mm^3) 310.2 ± 136.4; 71% men Economic status of participants not reported	No treatment: n = 5 in intervention group and n = 8 in placebo group; 1 NRTI: n = 3 in intervention group and n = 4 in placebo group; 2 NRTI: n = 11 in intervention group and n = 6 in placebo group; 1 NRTI + 1PI: n = 2 in intervention group and n = 0 in placebo group; 2 NRTI + 1 PI: n = 1 in intervention group and n = 4 in placebo group; 3 NRTI: n = 0 in intervention group and n = 1 in placebo group; 2 PI: n = 0 in intervention group and n = 1 in placebo group.

Sattler et al. (2008) [45]	USA; from February to December, 1999	RDB	59 PLWH Intervention group: n = 29; 41 (31 to 66) years old; proportion of participants according to CD4 (count/mm^3): < 200: n = 6; between 200-500: n = 16; > 500: n = 7; 90% men Control group: n=30; 41 (26 to 58) years old; proportion of participants according to CD4 (count/mm^3): < 200: n = 2; between 200-500: n = 19; > 500: n = 8; 87% men Economic status of participants not reported	PI + NRTI: n = 16 in intervention group and n = 17 in control group; PI+ NRTI + NNRTI: n = 8 in intervention group and n = 7 in control group; NRTI + NNRTI: n = 4 in intervention group and n = 3 in control group; only NRTI: n = 0 in intervention group and n = 2 in control group; PI + NNRTI: n = 1 in intervention group and n=0 in control group; without ART: n = 1 in control group.
Sakkas et al. (2009) [46]	USA; between August 2001 and January 2004	RDB	33 men PLWH Intervention group: n = 17; 44 ± 9 years old; CD4 (count/mm^3) 448 ± 310 Placebo group: n = 16; 44 ± 8 years old; CD4 (count/mm^3) 460 ± 278 Economic status of participants not reported	Different combinations of PI, NTRI and NNTRI. The authors referred to no significant differences in the ART schemes between the groups. Both groups included participants with no RT, but the number was not provided by the authors
Nyamathi et al. (2013) [47]	India (Data collection time not reported)	ROL	68 women PLWH Intervention group: n = 34; 32.2 ± 5.3 years old; CD4 (count/mm^3) = 439.1 ± 217.6. Control group: n = 34; 30.1 ± 5.2 years old; CD4 (count/mm^3) = 447.5 ± 260 Low-to-middle income country, with socio-cultural disparities	The authors only refer to the use of ART for at least three months, without specify the type of drugs combination.

Legend: ROL: Randomized Open Label; RDB: Randomized Double Blinded; PLWH: People Living with HIV; PIs = Protease inhibitors; ART: Antiretroviral therapy; NRTI: Nucleoside reverse-transcriptase inhibitors; NNRTI: Non-Nucleoside reverse-transcriptase inhibitors; OKG: I-ornithine-α-ketoglutarate.

Table 3. Main information about the interventions and results of the studies included in the SR.

Author (year) [ref]	Intervention	Control or placebo group	Duration	Information about control of PA and D	Information about side effects of the intervention	BC method	Main results	Conclusion (related to our SR)
Pichard et al. (1998) [41]	High-casein protein supplementation (33.6 g) with L-arginine (7.4 g) and omega-3 (1.7 g)	High-casein protein supplementation (26 g) without L-arginine or omega-3	6-months	PA - Not informed D - 3-day written food intake diaries	Intolerance by 5 participants from the Arg-omega-3 group and by 4 participants from control group; all of them dropped-out of the study	BIA	FFM (kg): Intervention group = from 14.7 to 15.0 Control group = from 14.1 to 14.7; no significant differences between groups	Supplementation with casein, added or not with L-arginine and omega-3, was ineffective in improving the FFM
Schwenk et al. (1999) [42]	Soy protein supplementation + nutritional counseling	Nutritional counseling only (written list of options to increase the energy intake	8-weeks	PA - Not reported D - Food intake assessed by 24 h food recall	No side-effects reported	BIA	<u>FFM (AUC%):</u> Intervention group = + 1.6 ± 4.5; Control group = +3.8 ± 6.2; p = 0.27 between groups	Soy protein supplementation did not improve the FFM
Agin et al. (2001) [43]	Whey protein ($1\ g^{-1}kg^{-1}d^{-1}$) of undenatured bovine derived whey protein powder)	Only resistance training	14-week intervention, with intervals of 6-week (control period); 20-week total time	PA - Progressive resistance training D - in-depth face-to-face and telephone interviews conducted by a trained registered dietitian	One patient in the PRO-PRE group complained of nausea when consuming the protein mixture but tolerated a half dose at 0.5 g/kg per day for the entire treatment	DEXA and MRI	<u>FFM from DEXA (kg):</u> PRO group = +1.4 ± 1.4 (p = 0.01 from baseline); Group PRE = + 1.6 ± 2.4 (p = 0.06 from baseline); Group PRO + PRE = 1.4±2.0 (p = 0.05 from baseline); No differences between groups <u>MM from MRI (kg):</u>	Whey protein ingested without physical training did not improve the muscle mass; in turn, resistance exercise training improved muscle mass; there was no additional effects with protein supplementation to the exercise effects.

							Group PRO = + 0.6 ± 1.1 (p = 0.12 from baseline); Group PRE = + 1.2 ± 0.69 (p < 0.001 from baseline); Group PRO + PRE = + 0.6 ± 1.6 (p = 0.30 from baseline); No differences between groups	
Karsegard et al. (2004) [44]	L-ornithine-α-ketoglutarate (1.3 g of nitrogen)	Placebo composed by isonitrogenous (with milk protein)	12-weeks	PA - by use of pedometers (results not shown in the paper) D - 3 food records, sent by mail to the participants 1 week before each evaluation	GI events occurred more frequently in the intervention group than in the placebo group (numbers not provided)	BIA	FFM (kg): Intervention group = from 46.1 ± 10.1 to 46.7 ± 10.3 (p > 0.05 from baseline) Placebo group = from 51.6 ± 10.8 to 51.8 ± 10.5 (p > 0.05 from baseline); no significant differences between groups	Supplementation with OKG did not improve the nutritional, functional, and immune status of PLWH
Sattler et al. (2008) [45]	High-whey-protein supplement (Biomune System®)	Isocaloric placebo	12-weeks (data collection at 6 and 12 weeks)	PA - Not informed D - 3-day written food intake diaries	Gastrointestinal disorders in 15 subjects in intervention group	BIA	LBM (kg): Intervention group = 54.2 ± 7.4 at baseline; 54.3 ± 7.3 at 6 weeks; 54.4 ± 7.0 at 12 weeks (p > 0.05 only time effect) Control group = 54.1 ± 5.7 at baseline; 54.5 ± 6.1 at week 6; 53.9 ± 6.1 at 12 weeks (p > 0.05 only time effect);	Whey protein was ineffective in improving LBM in weight stable PLWH

							group effect not significant	
Sakkas et al. (2009) [46]	Physical resistance exercise training (PRT) plus Creatine (loading phase of 4 daily doses of 5 g and maintenance dose with 2 daily doses of 2.4 g) Intake of creatine together with a fruit juice beverage containing 20 g of carbohydrates	PRT + Placebo (not specified)	13-weeks	PA - Physical resistance training was one intervention group D - No dietary information	One dropout in intervention group due to hypersensitivity reaction	DXA and MRI	LBM by DEXA (kg): Creatine group plus PRT = +2.3 ± 1.4 ($p < 0.05$ from baseline) Placebo group plus PRT = + 0.9 ± 1.4 ($p = 0.05$ from baseline); difference between groups = 1.4 (0.3 – 2.4); $p < 0.05$ Thigh muscle CSA by MRI (cm^2): Creatine group plus PRT = +12.2 ± 7.8 ($p < 0.05$ from baseline) Control group plus PRT: + 9.3 ± 8.1 ($p < 0.05$ from baseline); No differences between groups at 14 weeks (p value is not described) Calf muscle CSA (cm^2): Creatine group plus PRT = + 1.5 ± 3.8 Placebo group plus PRT = + 0.1 ± 3.5; no differences within and between group at 14 weeks (p value is not described)	Creatine supplementation showed additional benefits to physical resistance exercise training only by DXA analysis, but not by MRI analysis
Nyamathi et al. (2013) [47]	High protein Indian food-based	Usual care: Chana dal, based on	6-months	PA - Not informed	No side-effect reported	BIA	LBM (kg):	Protein supplementation

	supplement (Urad dal, based on lentils; Toor dal, based on peas. The participants also received educational program sessions	chickpeas. The participants received ther same number of educational session as the intervention group. However, with more general content		D - Food intake was not assessed			Intervention group: 33.4 ± 5.2 at baseline; 33.7 ± 6.2 at 3 months and 36.1 ± 4.9 at 6 months. Control group = baseline 31.8 ± 5.4 at baseline; 31.8 ± 6.0 at 3 months and 30.8 ± 6.1 at 6 months; p-value of the interaction between change over time and group= 0.0045 <u>Results Stratified by group with 66% or more adherence to ART</u> Intervention group = 34.4 ± 5.0 at baseline; 36.9 ± 4.7 at 3 months and 34.8 ± 4.6 at 6 months Control group = 32.9 ± 6.5 at baseline, 31.9 ± 7.2 at 3 months and 31.1 ± 7.5 at 6 months; p-value of the interaction between change over time and group = 0.0002	associated with educational support improved LBM, especially in those with greater adherence to ART

Legend: AUC = Area under the curve; BIA = Bioelectrical impedance; BC = Body composition; CSA = Cross Section Area; c^2 = Square centimeters; D = Diet; DXA = Dual-energy X-ray absorptiometry; FFM = Fat-free mass; g = grams; GI = Gastrointestinal; Kg = kilograms; Kcal = Kilocalories; LBM = Lean body mass; MM = Muscle mass; MR = Magnetic resonance; OKG = Ornithine and alpha-ketoglutarate; PA = Physical Activity; PLWH = People living with HIV; PRT = progressive resistance training; RM = 1 maximum repetition.

Supplementary table 1. Risk of bias analysis based on Cochrane manual.

	Pichard et al. (1998) [41]	Schwenk et al. (1999) [42]	Agin et al. (2001) [43]	Karsegard et al. (2004) [44]	Sattler et al. (2008) [45]	Sakkas et al. (2009) [46]	Nyamathi et al. (2013) [47]
1. Bias arising from the randomization process							
1.1. Was the allocation sequence random?	Y(=low)	PY(=low)	Y(=low)	Y(=low)	Y(=low)	Y(=low)	PY (=low)
1.2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	PY(=low)	NI	PY (=low)	PY(=low)	Y (=low)	PY(=low)	N (=high)
1.3. Did baseline differences between intervention groups suggest a problem with the randomization process?	N (=low)	N (=low)	N(=low)	N(=low)	N (=low)	N(=low)	PY(=high)
Risk-of-bias judgment (low/high/some concerns)	***Low risk***	***Some concerns***	***Low risk***	***Low risk***	***Low risk***	***Low risk***	***High risk***
What is the predicted direction of bias arising from the randomization process?		Few information about the randomization process; open label study			-		The study was open-label
2. Bias due to deviations from intended interventions							

2.1. Were participants aware of their assigned intervention during the trial?	N (=low)	Y (=high)	PY(=high)	N(=low)	N (=low)	PN(=low)	Y (=high)
2.2. Were careers and people delivering the interventions aware of participants' assigned intervention during the trial?	N (=low)	Y (=high)	PY(=high)	N(=low)	PY (=high)	PN(=low)	Y (=high)
2.3.Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NA	N (=low)	Y(=high)	N(=low)	N(=low)	NA	N (=low)
2.4. If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	NA	NA	PN(=low)	NA	NA	NA	NA
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA	NA	NA	NA	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI	N (=high)	Y(=low)	Y(=low)	Y(=low)	Y(=low)	N (=high)
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze	N (=low)	PY (=high)	NA	NA	NA	NA	PN (=low)

participants in the group to which they were randomized?							
Risk-of-bias judgment (low/high/some concerns)	***Low risk***	***High risk***	***Some concerns***	***Low risk***	***Some concerns***	***Low risk***	***High risk***
What is the predicted direction of bias due to deviations from intended interventions?		The trial was not blinded	The blindness of the study was not clearly described		The study probably was not blinded to the researchers		The study was not planned to be blinded
3. Bias due to missing outcome data							
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y(=low)	NI	Y(=low)	N(=high)	Y (=low)	N(=high)	Y(=low)
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA	NA	PN (=high)	NA	PN(=high)	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA	NA	PN(=low)	NA	PN(=low)	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA	NA	NA	NA	NA
Risk-of-bias judgment (low/high/some concerns)	***Low risk***	***Some concerns***	***Low risk***	***High risk***	***Low risk***	***High risk***	***Low risk***

What is the predicted direction of bias due to deviations from intended interventions?		There is no information about missing data		Although the authors conducted the analysis as intended to treat, the number of dropouts was too high	The analysis included nearly all the participants and missing data were appropriately treated	The authors did not conduct an intention to treat analysis	The sample was maintained throughout the experiment
4. Bias in measurement of the outcome							
4.1 Was the method of measuring the outcome inappropriate?	N(=low)	N (=low)	N(=low)	N(=low)	N (=low)	N(=low)	N (=low)
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N(=low)	N (=low)	N(=low)	N(=low)	N (=low)	N(=low)	N (=low)
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N(=low)	NI	PY(=high)	PN(=low)	PY (=high)	PN(=low)	Y (=high)
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	PY (=high)	PN (=low)	PN(=low)	PY (=high)	NA	PY (=high)
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was	NA	PY (=high)	NA	NA	PY (=high)	NA	PY (=high)

influenced by knowledge of intervention received?							
Risk-of-bias judgment (low/high/some concerns)	***Low risk***	***Some concerns***	***Some concerns***	***Low risk***	***High risk***	***Low risk***	***High risk***
What is the predicted direction of bias due to deviations from intended interventions?		There is no information about the blindness of assessors	The blindness of the study was not clearly described		The assessors probably were not blinded to the study		The study was open-label
5. Bias in selection of the reported result							
5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y(=low)	NI	Y(=low)	Y(=low)	Y(=low)	Y(=low)	Y (=low)
Is the numerical result being assessed likely to have been selected, on the basis of the results, from							
5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	N(=low)	N (=low)	N(=low)	N(=low)	N(=low)	N(=low)	N (=low)
5.3 ... multiple eligible analyses of the data?	N(=low)	N (=low)	N(=low)	N(=low)	N(=low)	N(=low)	N (=low)

Risk-of-bias judgment (low/high/some concerns)	***Low risk***	***Some concerns***	***Low risk***	***Low risk***	***Low risk***	***Low risk***	***Low risk***
What is the predicted direction of bias due to deviations from intended interventions?	The study was conducted according to the planning	There was not blindness in the study			The study was conducted according to the planning		The study was conducted according to the planning
Overall bias							
Overall Risk-of-bias judgment (low/high/some concerns)	***Low risk***	***Some concerns***	***Some concerns***	***Some concerns***	***Some concerns***	***Some concerns***	***Some concerns***
What is the overall predicted direction of bias due to deviations from intended interventions?		There was not enough information to be sure about the risk of bias	The blindness of the study was not clearly described	Despite of the intention to treat analysis, the rate of dropouts was too high	The assessors possibly were not blinded to the study	The authors did not conduct an intention to treat analysis	Despite of some aspects being evaluated as high risk, the local conditions of the study were very typical, and did not allow different evaluations

Figure 1. Flow chart of the systematic review.

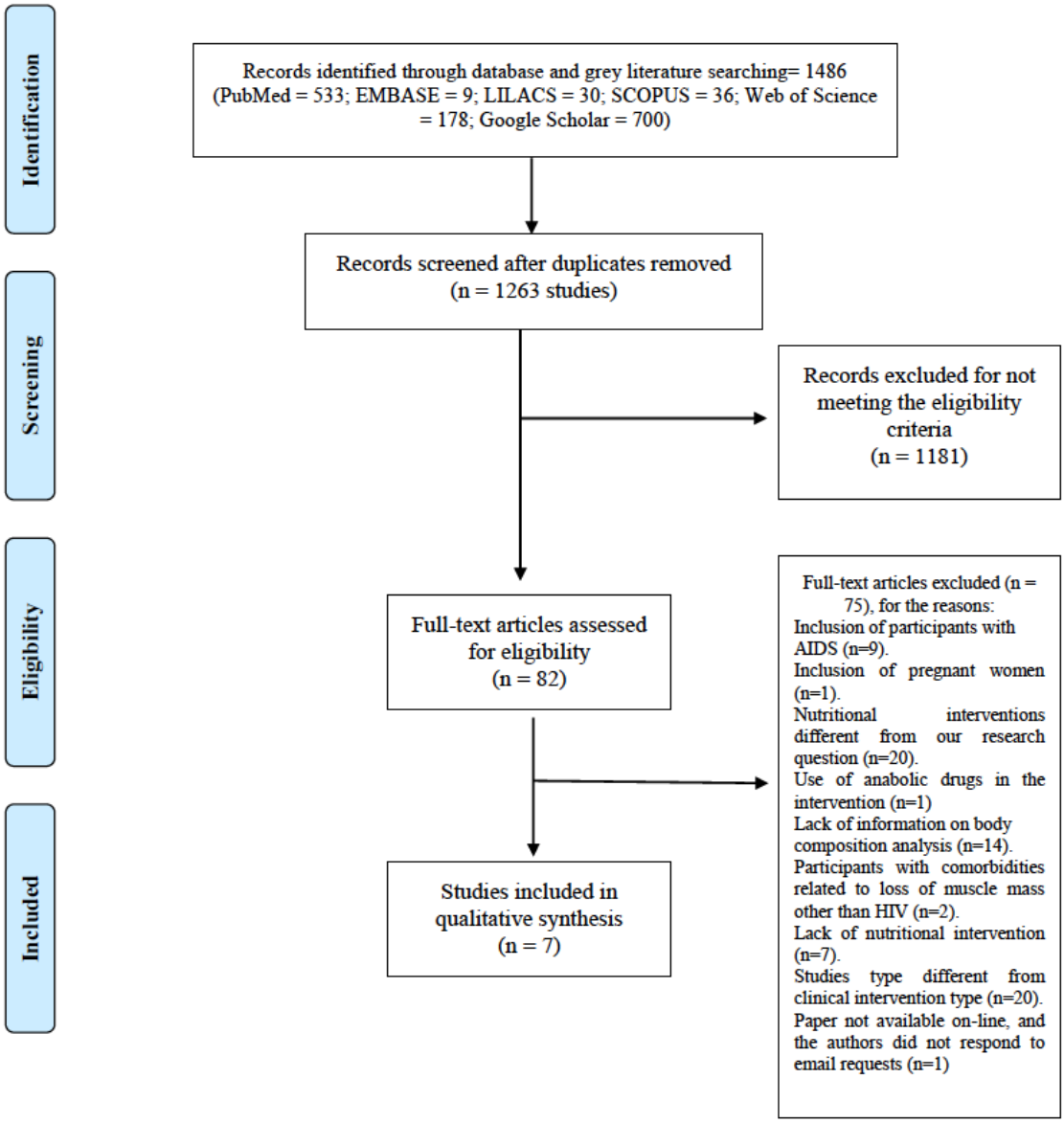

Figure 2. Assessment of risk of bias of individual articles.

Author (year) [ref]	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in the measurement of the outcome	Bia in the selection of the reported result	Overall risk of Bias	
Pichard et al. (1998) [41]	+	+	+	+	+	+	Low risk
Schwenk et al. (1999) [42]	?	−	?	?	?	?	Some concerns
Agin et al. (2001) [43]	+	?	+	?	+	?	Some concerns
Karsegard et al. (2004) [44]	+	+	−	+	+	?	Some concerns
Sattler et al. (2008) [45]	+	?	+	−	+	?	Some concerns
Sakkas et al. (2009) [46]	+	+	−	+	+	?	Some concerns
Nyamathi et al. (2013) [47]	−	−	+	−	+	?	Some concerns

7 CONCLUSÃO E CONSIDERAÇÕES FINAIS

Com base nos achados obtidos, podemos concluir que as PVHIV apresentam um perfil mais suscetível para desordens musculares, especialmente, pelo efeito residual do próprio vírus e das suas proteínas acessórias, que colaboram para persistente imunoativação e ISBG. Além disso, apesar da necessidade de utilização das TARVs para controle da replicação viral e manutenção do estado de saúde, seu uso proporciona efeitos adversos que afetam o metabolismo lipídico e muscular, ambos relacionados à manutenção da ISBG e ao balanço proteico muscular negativo. Ademais, os estudos que avaliaram a prevalência de sarcopenia em PVHIV utilizaram critérios variados, predominando o uso exclusivo da redução do índice da massa muscular apendicular.

Os resultados dos estudos transversais revelaram que as PVHIV apresentaram maior frequência de risco de sarcopenia e uma pior qualidade de vida relacionada à sarcopenia comparativamente às PNVHIV. No grupo de PVHIV, entre as pessoas que estão sob risco de sarcopenia, a qualidade de vida relacionada à sarcopenia foi menor comparativamente às pessoas que não estão sob risco de sarcopenia. Os principais fatores associados à pior qualidade de vida relacionada à sarcopenia foram pior qualidade do sono e viver com obesidade, ao passo que a prática de exercícios físicos foi o principal fator associado à menor chance de pertencer ao grupo menor qualidade de vida associada à sarcopenia.

Ademais, dentre os parâmetros objetivos para determinação da sarcopenia, pode-se observar que as PVHIV apresentaram menor força muscular em comparação às PNVHIV. Por outro lado, a massa muscular e o desempenho físico não foram diferentes entre os grupos. Ainda, pode-se verificar que as PVHIV apresentaram menor qualidade muscular comparativamente às PNVHIV. Neste sentido, pode-se verificar, considerando os constructos aplicados para definir sarcopenia, que de modo geral as pessoas avaliadas não foram consideradas sarcopênicas, refutando a nossa principal hipótese.

Entretanto, aplicando apenas o critério de menor força muscular, as PVHIV apresentaram maior frequência de dinapenia em comparação às PNVHIV, independentemente do critério utilizado. Considerando a frequência de obesidade dinapênica, apenas com um dos constructos pode-se verificar que as PVHIV apresentaram maior frequência desta condição. Não foram observadas diferenças na dinapenia associada à obesidade central entre os grupos.

Viver com HIV e apresentar maior razão entre a gordura corporal e a massa magra foram os fatores mais associados à menor força muscular. Ainda, apenas entre as PVHIV, a maior

razão entre a gordura corporal e a massa magra foi a principal variável associada à menor força muscular.

Considerando a massa muscular, ao contrário da nossa hipótese inicial, viver com HIV foi associado a maior quantidade do IMMA, ao passo que na análise apenas com PVHIV, nenhuma variável testada foi associada à menor quantidade do IMMA; contudo, é fundamental destacar que as diferenças médias entre o IMMA do grupo de PVHIV e PNVHIV é pequena, implicando em pequeno tamanho de efeito, poder e tamanho amostral baixo para essas comparações.

No que tange o uso de antirretrovirais, não verificamos diferenças no grau de associação para força e massa muscular entre os esquemas utilizados atualmente. O tempo de infecção e de tratamento também não foram associados à força e a massa muscular. Contudo, o uso de ritonavir foi associada à menor quantidade de massa muscular, enquanto o uso prévio de zidovudina foi associado ao maior índice de gordura corporal e à maior razão gordura corporal: massa magra.

Finalmente, as intervenções nutricionais que envolveram o consumo de proteínas intactas, aminoácidos isolados e compostos nitrogenados não foram capazes de promover efeitos positivos sobre os parâmetros relacionados à massa muscular avaliados em PVHIV. Todavia, os dados provenientes destes estudos devem ser interpretados com cautela, tendo em vista a heterogeneidade dos métodos utilizados para avaliar a composição corporal, assim como, as fragilidades metodológicas no delineamento dos estudos.

É importante reforçar que os nossos achados são provenientes de estudos transversais, não possibilitando inferir causalidade, bem como o tamanho e poder da amostra não permitem extrapolações antecipadas e os resultados devem ser interpretados com cautela. Além disso, as amostras apresentam diferenças que não podem ser controladas estatisticamente, sendo assim, no futuro, estudos que consigam controlar outras variáveis associadas ao HIV são indispensáveis para melhor compreender as hipóteses relacionadas à sarcopenia. Portanto, novos estudos, sobretudo, com maior número de pessoas e longitudinais, possibilitarão confirmar o conceito de envelhecimento antecipado nesta população, principalmente no que se refere às alterações musculares que podem incorrer em sarcopenia.

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APÊNDICES

Apêndice A – Questionário utilizado para coleta de dados da pesquisa online

PERGUNTAS DECISÓRIAS

Primeiro gostaríamos de saber:

Você reside no município de São Paulo?

( ) Não *[questionário é encerrado]*

( ) Sim

Você vive com HIV?

( ) Não

( ) Sim

DADOS SOCIODEMOGRÁFICOS E DE SAÚDE

Seção 1 – Dados Pessoais e Sociodemográficos

1. Nome Completo: _____

2. Data de nascimento: ____/____/_____

3. Cor/etnia:
   ( ) Branca
   ( ) Preta/Negra
   ( ) Parda
   ( ) Outro:_____
   ( ) Prefiro não responder

4. Sexo ao seu nascimento:
   ( ) Feminino
   ( ) Masculino
   ( ) Intersexual

( ) Prefiro não responder

5. Com qual gênero você se identifica?
   ( ) Feminino
   ( ) Masculino
   ( ) Outro:_____
   ( ) Prefiro não responder

6. Orientação sexual:
   ( ) Homossexual
   ( ) Heterossexual
   ( ) Bissexual
   ( ) Outro:_____
   ( ) Prefiro não responder

7. Trabalha atualmente?
   ( ) Não
   ( ) Sim
   ( ) Prefiro não responder

8. Ocupação:_____

9. Última série/grau COMPLETO que cursou:
   ( ) Curso primário
   ( ) Admissão
   ( ) Curso ginasial ou ginásio
   ( ) 1º grau ou fundamental ou supletivo de 1º grau
   ( ) 2º grau ou colégio ou técnico ou normal ou científico ou ensino médio ou supletivo de 2º grau
   ( ) 3º grau ou curso superior
   ( ) Pós-graduação (especialização, mestrado, doutorado)
   ( ) Nunca estudei
   ( ) Prefiro não responder

10. Renda mensal:
    ( ) < 1 salário mínimo;
    ( ) 1 a 2 salários mínimos;
    ( ) 2 a 3 salários mínimos;
    ( ) 3 a 4 salários mínimos;
    ( ) 5 a 9 salários mínimos;
    ( )10 ou mais
    ( ) Prefiro não responder

Seção 2 – Saúde e hábitos de vida

11. Você tem diagnóstico pelo médico de hipertensão arterial (pressão alta)?
    ( ) Não
    ( ) Sim
    ( ) Prefiro não responder

12. Você tem diagnóstico pelo médico de alteração do colesterol?
    ( ) Não
    ( ) Sim
    ( ) Prefiro não responder

13. Você tem diagnóstico pelo médico de diabetes?
    ( ) Não [*pula para a questão 15*]
    ( ) Sim
    ( ) Prefiro não responder

14. Qual tipo de diabetes?
    ( ) Tipo 1
    ( ) Tipo 2
    ( ) Prefiro não responder

15. Você tem diagnóstico de alguma doença gastrintestinal (como gastrite, úlcera, doença celíaca, etc.)?
    ( ) Não [*pula para a questão 17*]
    ( ) Sim

( ) Prefiro não responder

16. Qual doença gastrintestinal?_____

17. Você tem algum problema nos olhos, como dificuldade de enxergar de longe, dificuldade de ler, ou doenças oculares?
    ( ) Não *[pula para questão 19]*
    ( ) Sim
    ( ) Prefiro não responder

18. Você utiliza algum dispositivo/auxílio para seu o problema ocular (exemplos: óculos de grau, lentes de contato, lupa, cão guia, entre outros)?
    ( ) Não
    ( ) Sim
    ( ) Prefiro não responder

19. Você tem algum problema de audição?
    ( ) Não *[pula para questão 21]*
    ( ) Sim
    ( ) Prefiro não responder

20. Você utiliza algum dispositivo/auxílio para o seu problema de audição (exemplo: aparelho auditivo, entre outros)?
    ( ) Não
    ( ) Sim
    ( ) Prefiro não responder

21. Atualmente, você fuma algum produto do tabaco?
    ( ) Sim, diariamente
    ( ) Sim, menos que diariamente
    ( ) Não fumo atualmente
    ( ) Prefiro não responder

22. E no passado, você fumou algum produto do tabaco diariamente?
    ( ) Não
    ( ) Sim

( ) Prefiro não responder

23. Com que frequência você costuma consumir alguma bebida alcoólica?
( ) Não bebo nunca [*pula para a questão 26*]
( ) Menos de uma vez por mês [*pula para a questão 25*]
( ) Uma vez ou mais por mês
( ) Prefiro não responder

24. Quantos dias por semana você costuma consumir alguma bebida alcoólica?
( ) Nunca ou menos de 1 vez ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5 ( ) 6 ( ) 7
( ) Prefiro não responder

25. Utilize as informações desta imagem para basear sua resposta da próxima pergunta, considerando que uma dose equivale a:

Em geral, no dia que você bebe, quantas **doses** de bebida alcoólica você consome? (*uma dose de bebida alcoólica equivale a uma lata de cerveja, uma taça de vinho, uma dose de cachaça, whisky ou qualquer outra bebida alcoólica destilada, como demonstrado na figura acima)*

( ) Menos de 1 dose ( ) 1 ( ) 2 ( ) 3 ( ) 4 ( ) 5 ( ) 6 ou mais doses
( ) Prefiro não responder

26. Qual seu peso atual? (em kg) _____

27. Qual sua altura? (em centímetros) _____

28. Você perdeu mais de 3 kg sem querer nos últimos meses?
( ) Não

( ) Sim

( ) Prefiro não responder

29. Você vem tendo perda de apetite?

( ) Não

( ) Sim

( ) Prefiro não responder

30. Você recebeu algum tipo de aconselhamento sobre nutrição (mesmo que de forma remota) durante a pandemia da COVID-19?

( ) Não

( ) Sim

( ) Prefiro não responder

31. Você recebe, atualmente, algum tipo de aconselhamento sobre alimentação? (nutricionista, médico etc.)

( ) Não

( ) Sim

( ) Prefiro não responder

Seção 3 – COVID-19

32. Teve diagnóstico médico para COVID-19?

( ) Não *[pula para questão 35]*

( ) Sim

( ) Prefiro não responder

33. Você precisou ser hospitalizado?

( ) Não *[pula para questão 36]*

( ) Sim

( ) Prefiro não responder

34. Você foi entubado?

( ) Não

( ) Sim

( ) Prefiro não responder

35. Qual das seguintes opções descreve melhor seu comportamento durante o período de distanciamento social devido ao coronavírus (COVID-19)?

( ) Fiquei em isolamento total, não saía de casa, e não tive contato com nenhuma outra pessoa, exceto as pessoas que moram comigo.

( ) Saía apenas para fazer serviços obrigatórios, como trabalhar, ou essenciais, como ir à farmácia, médico, comprar alimentos.

( ) Eu evitava aglomerações e locais públicos, mas saía para serviços NÃO essenciais.

( ) Eu continuei saindo normalmente como já fazia antes do distanciamento social. *[pula para questão 37]*

( ) Prefiro não responder

36. Com relação ao comportamento descrito na questão anterior, quanto tempo ele durou ou dura?

( ) menos de 3 meses

( ) entre 3 e 6 meses

( ) entre 6 meses e 1 ano

( ) mais de 1 ano, mas já não estou mais em distanciamento

( ) mais de um ano, e ainda estou em distanciamento social

( ) Prefiro não responder

37. Você já foi vacinado contra a COVID-19?

( ) Não

( ) Já, mas apenas a primeira dose

( ) Já tomei as duas doses, ou a vacina que tomei é de dose única

( ) Não pretendo me vacinar

( ) Prefiro não responder

EXERCÍCIO FÍSICO, ATIVIDADE FÍSICA E COMPORTAMENTO SEDENTÁRIO

Seção 1 – Exercício Físico

As perguntas abaixo estão relacionadas à prática de exercícios físicos. Entenda exercício físico como algo planejado e estruturado, que faz parte da sua rotina diária ou semanal. Portanto, esses exercícios físicos estão distribuídos na sua rotina, tem um tempo médio para realização e uma frequência semanal.

38. Qual tipo de exercício físico você realiza?

( ) Endurance *(caminhada [exceto para o trabalho] ou corrida, bicicleta ou bicicleta ergométrica, natação ou hidroginástica, ginástica aeróbica [spinning, step ou jump], esportes coletivos como futsal/futebol, vôlei, basquetebol e handebol, artes marciais e luta, aula de dança etc.)*

( ) Força *(musculação, crossfit®, exercício funcional, pilates ou calistenia)*

( ) Ambos

( ) Não pratico exercício físico *[pula para questão 75]*

( ) Prefiro não responder

39. Qual frequência semanal você faz esses exercícios físicos?

( ) 1x/semana

( ) 2-3x/semana

( ) 4-5x/semana

( ) 6-7x/semana

( ) Prefiro não responder

40. Por quanto tempo você faz esse exercício físico no dia?

( ) 10-20 minutos/dia

( ) 21-40 minutos/dia

( ) 41-60 minutos/dia

( ) > 1 hora/dia

( ) Prefiro não responder

Seção 2 – Comportamento Sedentário

As perguntas a seguir são relacionadas ao tempo em que você permanece sentado (a) todo dia utilizando dispositivos eletrônicos por lazer ou por trabalho. Não inclua o tempo gasto sentado durante o transporte em ônibus, trem, metrô ou carro.

41. Quanto tempo você normalmente permanece sentado (a) assistindo televisão em **DIA DE SEMANA**? Calcule uma média de horas por dia.

_____

42. Quanto tempo você normalmente permanece sentado (a) assistindo televisão em dia de **FINAL DE SEMANA**? Calcule uma média de horas por dia.

_____

43. Quanto tempo você normalmente permanece sentado (a) usando celular, videogame ou computador durante um **DIA DE SEMANA**? Calcule uma média de horas por dia.

_____

44. Quanto tempo você normalmente permanece sentado (a) usando o celular, videogame ou computador durante um dia de **FINAL DE SEMANA**? Calcule uma média de horas por dia.

_____

ANEXOS

ANEXO A - PARECER CONSUBSTANCIADO DO CEP – Projeto Rastreio de sarcopenia, alterações cognitivas e relações com estilo de vida em pessoas vivendo com o vírus da imunodeficiência humana em terapia antirretroviral: um estudo transversal.

USP - FACULDADE DE SAÚDE PÚBLICA DA UNIVERSIDADE DE SÃO PAULO - FSP/USP

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Rastreio de sarcopenia, alterações cognitivas e relações com estilo de vida em pessoas vivendo com o vírus da imunodeficiência humana em terapia antirretroviral: um estudo transversal

Pesquisador: Sandra Maria Lima Ribeiro

Área Temática:

Versão: 1

CAAE: 50663721.0.0000.5421

Instituição Proponente: Faculdade de Saúde Pública da Universidade de São Paulo - FSP/USP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.938.460

Apresentação do Projeto:

As informações elencadas nos campos "Apresentação do Projeto", "Objetivos da Pesquisa" e "Avaliação de Riscos e Benefícios" foram retiradas do arquivo de informações básicas do projeto PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1805957.pdf e do projeto de pesquisa, do arquivo Projeto_SEAP_online2_TCLE.docx, na sua 1a. versão de 9/8/2021."Trata-se de um estudo descritivo, exploratório, transversal e observacional a ser realizado em PVHA e pessoas que não vivem com o vírus (PVHAN).

Objetivo da Pesquisa:

"Investigar o risco de sarcopenia, de alterações cognitivas, depressivas, e a qualidade de vida em adultos e idosos vivendo com o vírus da imunodeficiência (HIV) em uso terapia antirretroviral (TARV), e comparar com um grupo sem o vírus".

Avaliação dos Riscos e Benefícios:

Riscos: a) constrangimento no momento de preencher as perguntas, tendo a opção de resposta "prefiro não responder". Além disso, também será ressaltado que o participante tem a opção de não responder o questionário até o final; b) Quebra do sigilo dos dados por hackeamento; para minimizar esse risco, será usada uma plataforma de coletas de dados que assegura o cumprimento à Lei Geral de proteção de dados (LGPD)(SurveyMonkey®).

Benefícios: A "pesquisa não possibilita benefícios imediatos aos participantes, no entanto,

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futuramente, essas informações poderão agregar para práticas preventivas mais assertivas, maximizando a chance de intervir precocemente em condições que afetam a qualidade de vida". "Pretende-se demonstrar a importância de se rastrear os riscos de e comprometimentos cognitivos nos atendimentos de saúde oferecidos a PVHA, no intuito de sugerir estratégias voltadas para alimentação, atividade física e qualidade do sono".

Comentários e Considerações sobre a Pesquisa:

"A amostra, não probabilística e de conveniência é composta por PVHA usuárias do ambulatório SEAP (Serviço de Extensão ao Paciente do HC da FM/USP) e serão contatas por aplicativo de mensagem; os dados para os contatos serão obtidos nos registros do serviço. As pessoas que demonstrarem interesse respondendo à mensagem convite, receberão o link para o questionário virtual (Apêndice A), hospedado na plataforma SurveyMonkey® (https://pt.surveymonkey.com/r/nafeusp). A resposta a esse questionário é a Etapa 1 do estudo. As PHAN (grupo controle) serão recrutadas ativamente por meio da divulgação em redes sociais, pelo método "bola de neve". Os respondentes serão convidados a participar da segunda etapa, que consiste na investigação aprofundada da dieta e da atividade física. Pretende-se avaliar uma subamostra de 100 pessoas por grupo. A etapa 3 consiste na aplicação de uma bateria de testes neuropsicológicos e a etapa 4 consiste na aplicação de testes físicos e coleta de material biológico. Essas etapas são integradas ao presente estudo para avaliações mais aprofundadas e robustas sobre as perguntas de pesquisa. Todavia, elas fazem parte de outros dois projetos de pesquisa que já têm aprovação pelos comitês de ética. São eles: FSP/USP parecer no.3.100.32 de 19/12/2018 e Universidade São Judas Tadeu parecer no.4.763.071 de 9/6/2021. Critério de Inclusão: idade maior ou igual a 18 anos, ambos os sexos, residência no município de São Paulo. Especificamente para PVHA serão incluídos apenas aqueles com carga viral indetectável; em uso contínuo da terapia antirretroviral.

Considerações sobre os Termos de apresentação obrigatória:

Adequados.

Recomendações:

Pela aprovação.

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências.

Considerações Finais a critério do CEP:

Ressalta-se que cabe ao pesquisador responsável encaminhar os relatórios parciais (de 6 em 6 meses) e final da pesquisa, por meio da Plataforma Brasil, via notificação do tipo "relatório" para

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que sejam devidamente analisados pelo CEP.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1805957.pdf	10/08/2021 17:32:37		Aceito
Folha de Rosto	folhaDeRosto_ass_sandra_marly.pdf	10/08/2021 17:31:39	Sandra Maria Lima Ribeiro	Aceito
Declaração de concordância	carta_anuencia_SEAP.pdf	10/08/2021 17:31:27	Sandra Maria Lima Ribeiro	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Projeto_SEAP_online2_TCLE.docx	09/08/2021 16:30:31	Sandra Maria Lima Ribeiro	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_SEAP_online_06ago.docx	09/08/2021 16:30:09	Sandra Maria Lima Ribeiro	Aceito
Cronograma	Projeto_SEAP_online2_cronograma.docx	09/08/2021 16:29:29	Sandra Maria Lima Ribeiro	Aceito
Brochura Pesquisa	Projeto_SEAP_online_brochura.docx	09/08/2021 16:29:17	Sandra Maria Lima Ribeiro	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 28 de Agosto de 2021

Assinado por:
Kelly Polido Kaneshiro Olympio
(Coordenador(a))

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ANEXO B – Questionário de rastreio de sarcopenia - SARC - F

ID:	**Nome Completo:**

RASTREIO DE SARCOPENIA

Componente	**Pergunta**	**Pontuação**	**Resposta**
K10. Força	O quanto de dificuldade você tem para levantar e carregar 5kg?	Nenhuma = 0 Alguma = 1 Muita, ou não consegue = 2	
K11. Ajuda para caminhar	O quanto de dificuldade você tem para atravessar um cômodo?	Nenhuma = 0 Alguma = 1 Muita, usa apoios, ou incapaz = 2	
K12. Levantar da cadeira	O quanto de dificuldade você tem para levantar de uma cama ou cadeira?	Nenhuma = 0 Alguma = 1 Muita, ou não consegue sem ajuda = 2	
K13. Subir escadas	O quanto de dificuldade você tem para subir um lance de escadas de 10 degraus?	Nenhuma = 0 Alguma = 1 Muita, ou não consegue = 2	
K14. Quedas	Quantas vezes você caiu no último ano?	Nenhuma = 0 1 -3 quedas = 1 4 ou mais quedas = 2	
K15. Panturrilha	Checar nas medidas antropométricas	Mulheres: >33 cm = 0 ≤33 cm = 10 Homens: >34 cm = 0 ≤34 cm = 10	
K15a. Pontuação total:		**K15b. Classificação:**	

ANEXO C – Questionário de qualidade de vida associado a sarcopenia - SarQoL®

Questionário I Tempo: 10 min aproximadamente

SarQoL
Sarcopenia and Quality of Life

Qualidade de vida com sarcopenia

Este questionário tem perguntas sobre sarcopenia, uma fraqueza muscular que ocorre com o envelhecimento. A sarcopenia pode afetar sua vida diária. Esta pesquisa nos possibilita descobrir se o estado atual dos seus músculos afeta sua qualidade de vida.

Por favor, escolha a resposta mais apropriada para cada questão. O preenchimento do questionário deve levar aproximadamente 10 minutos.

1. Você atualmente sente diminuição:

	Muita	Alguma	Um pouco	Nenhuma
Na força de seus braços?	☐	☐	☐	☐
Na força de suas pernas?	☐	☐	☐	☐
Na sua massa muscular?	☐	☐	☐	☐
Na sua energia?	☐	☐	☐	☐
Nas suas capacidades físicas?	☐	☐	☐	☐
Na sua flexibilidade geral?	☐	☐	☐	☐

2. Você sente dor nos seus músculos?

☐	Frequentemente
☐	Algumas vezes
☐	Raramente
☐	Nunca

SarQoL
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3. Quando realiza atividades físicas leves (caminhar lentamente, passar roupa, tirar o pó, lavar louças, fazer artesanato, regar as plantas, etc.), você:

	Frequentemente	Às vezes	Raramente	Nunca	Eu não faço esse tipo de atividade física
Tem dificuldade?	☐	☐	☐	☐	☐
Fica cansado(a)?	☐	☐	☐	☐	☐
Sente dor?	☐	☐	☐	☐	☐

4. Quando realiza atividades físicas moderadas (caminhar rapidamente, lavar janelas, passar aspirador, lavar o carro, tirar mato do jardim, etc.), você:

	Frequentemente	Às vezes	Raramente	Nunca	Eu não faço esse tipo de atividade física
Tem dificuldade?	☐	☐	☐	☐	☐
Fica cansado(a)?	☐	☐	☐	☐	☐
Sente dor?	☐	☐	☐	☐	☐

5. Quando realiza atividades físicas intensas (correr, fazer trilhas, levantar objetos pesados, mover móveis, cavar no jardim, etc.), você:

	Frequentemente	Às vezes	Raramente	Nunca	Eu não faço esse tipo de atividade física
Tem dificuldade?	☐	☐	☐	☐	☐
Fica cansado(a)?	☐	☐	☐	☐	☐
Sente dor?	☐	☐	☐	☐	☐

6. Você atualmente se sente velho(a)?

- ☐ Sim, muito
- ☐ Sim, mais ou menos
- ☐ Sim, um pouco
- ☐ Não, nem um pouco

SarQoL
Sarcopenia and Quality of Life

7. Se respondeu sim na questão 6, o que te dá essa impressão?
(escolha todas as alternativas que quiser)

- ☐ Eu passo mal facilmente
- ☐ Eu tomo muitos remédios
- ☐ Eu sinto fraqueza nos meus músculos
- ☐ Eu tenho problemas de memória
- ☐ Eu já vivenciei a morte de muitas pessoas próximas
- ☐ Eu não tenho muita energia, me sinto cansado(a) frequentemente
- ☐ Eu não estou enxergando bem
- ☐ Outro: _____

8. Você se sente fisicamente fraco(a)?

- ☐ Sim, completamente
- ☐ Sim, mais ou menos
- ☐ Sim, um pouco
- ☐ Não, nem um pouco

9. Você se sente limitado:

	Muito	Um tanto	Um pouco	Nem um pouco
Em relação ao período de tempo que consegue caminhar?	☐	☐	☐	☐
Em quão frequentemente você sai para caminhar?	☐	☐	☐	☐
Em relação à distância que consegue caminhar?	☐	☐	☐	☐
Em relação à velocidade que consegue caminhar?	☐	☐	☐	☐
Em relação ao tamanho dos seus passos?	☐	☐	☐	☐

10. Quando está andando:

	Frequentemente	Às vezes	Raramente	Nunca	Eu não consigo andar
Você se sente muito cansado(a)?	☐	☐	☐	☐	☐
Você precisa se sentar regularmente para se recuperar?	☐	☐	☐	☐	☐
Você tem dificuldade para atravessar a rua rápido o suficiente?	☐	☐	☐	☐	☐
Você tem dificuldade com pisos irregulares?	☐	☐	☐	☐	☐

SarQoL
Sarcopenia and Quality of Life

11. Você tem problemas de equilíbrio?

- ☐ Frequentemente
- ☐ Ocasionalmente
- ☐ Raramente
- ☐ Nunca

12. Você cai com frequência?

- ☐ Muitas vezes
- ☐ Ocasionalmente
- ☐ Raramente
- ☐ Nunca

13. Você acha que sua aparência física mudou?

- ☐ Sim, muito
- ☐ Sim, mais ou menos
- ☐ Sim, um pouco
- ☐ Não, nem um pouco

14. Se respondeu sim à questão 13, de que forma? (escolha todas as alternativas que quiser)

- ☐ Mudança de peso (você ganhou ou perdeu peso)
- ☐ Surgimento de rugas
- ☐ Perda de altura
- ☐ Perda de massa muscular
- ☐ Queda de cabelo
- ☐ Surgimento de cabelos brancos
- ☐ Outro: _____

15. Se respondeu sim à questão 13, essa mudança o(a) incomoda?

- ☐ Sim, muito
- ☐ Sim, mais ou menos
- ☐ Sim, um pouco
- ☐ Não, nem um pouco

SarQoL
Sarcopenia and Quality of Life

16. Você se sente frágil?

- ☐ Muito
- ☐ Um pouco
- ☐ De forma alguma

17. Você está sentindo dificuldades para realizar qualquer uma das seguintes atividades diárias?

	Incapaz	Grande dificuldade	Alguma dificuldade	Nenhuma dificuldade	Não se aplica
Subir um lance de escadas	☐	☐	☐	☐	☐
Subir vários lances de escadas	☐	☐	☐	☐	☐
Subir um ou vários degraus sem segurar no corrimão	☐	☐	☐	☐	☐
Agachar ou ajoelhar	☐	☐	☐	☐	☐
Inclinar-se ou abaixar-se para pegar um objeto do chão	☐	☐	☐	☐	☐
Se levantar do chão sem segurar em nada	☐	☐	☐	☐	☐
Levantar-se de uma cadeira baixa sem apoio para os braços	☐	☐	☐	☐	☐
Mover-se, geralmente, de uma posição sentada para uma posição em pé	☐	☐	☐	☐	☐
Carregar objetos pesados (grandes sacolas cheias de compras, panela cheia de água, etc.)	☐	☐	☐	☐	☐
Abrir uma garrafa ou jarra	☐	☐	☐	☐	☐
Usar transporte público	☐	☐	☐	☐	☐
Entrar ou sair de um carro	☐	☐	☐	☐	☐
Fazer suas compras	☐	☐	☐	☐	☐
Fazer o serviço de casa (arrumar a cama, passar aspirador, passar roupa, lavar as louças, etc.)	☐	☐	☐	☐	☐

SarQoL
Sarcopenia and Quality of Life

18. A sua fraqueza muscular limita seus movimentos?

- ☐ Sim, muito
- ☐ Sim, mais ou menos
- ☐ Sim, um pouco
- ☐ Não, nem um pouco

19. Se respondeu sim à questão 18, por quais razões?
(escolha todas as alternativas que quiser)

- ☐ Medo de dor
- ☐ Medo de que você pode não conseguir
- ☐ Medo de se sentir cansado após essas atividades
- ☐ Medo de cair
- ☐ Outro: _____

20. Sua fraqueza muscular limita sua vida sexual?

- ☐ Eu não sou sexualmente ativo(a)
- ☐ Sim, completamente
- ☐ Sim, mais ou menos
- ☐ Sim, um pouco
- ☐ Não, nem um pouco

21. Como mudou sua participação em atividades físicas/esportes?

- ☐ Aumentou
- ☐ Diminuiu
- ☐ Não mudou
- ☐ Eu nunca fiz atividades físicas ou esportes

22. Como mudou sua participação em atividades de lazer (sair para comer, jardinagem, fazer artesanato, pescar, clubes da terceira idade, jogar baralho, fazer uma caminhada, etc.) ?

- ☐ Aumentou
- ☐ Diminuiu
- ☐ Não mudou
- ☐ Eu nunca participei de atividades de lazer

ANEXO D - Mini Sleep Questionnaire (MSQ)

As perguntas abaixo têm como objetivo verificar a qualidade do seu sono. *Por favor, assinale o número/ frequência que melhor descreve sua resposta:*

	1 Nunca	2 Muito Rara-mente	3 Rara-mente	4 Às Vezes	5 Frequen-temente	6 Muito Frequen-temente	7 Sempre
Você tem dificuldade para adormecer à noite?							
Você acorda de madrugada e não consegue adormecer novamente?							
Você toma remédios para dormir ou tranquilizantes?							
Você dorme durante o dia?							
Ao acordar de manhã, você ainda se sente cansado (a)?							
Você ronca à noite (que você saiba)?							
Você acorda durante à noite?							
Você acorda com dor de cabeça?							
Você sente cansaço sem nenhum motivo aparente?							
Você tem sono agitado? (Mudanças constantes de posição ou movimentos de pernas e braços)							

ANEXO E - PARECER CONSUBSTANCIADO DO CEP – Dieta, inflamação sistêmica e desfechos à saúde em pessoas que vivem com o vírus HIV em terapia antirretroviral: rastreio inicial para planejamento de um estudo clínico.

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PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Dieta, inflamação sistêmica e desfechos à saúde em pessoas que vivem com o vírus HIV em terapia antirretroviral: rastreio inicial para planejamento de um estudo clínico.

Pesquisador: Sandra Maria Lima Ribeiro
Área Temática:
Versão: 3
CAAE: 98089318.7.0000.5421
Instituição Proponente: Faculdade de Saúde Pública da Universidade de São Paulo - FSP/USP
Patrocinador Principal: FUNDACAO DE AMPARO A PESQUISA DO ESTADO DE SAO PAULO

DADOS DO PARECER

Número do Parecer: 3.100.321

Apresentação do Projeto:
Está versão responde a pendência anteriormente apresentada, onde pedia-se a adequação dos riscos nas informações básicas do projeto, que foi atendida.

Objetivo da Pesquisa:
Tendo como meta o desenvolvimento futuro de estratégias de intervenções não farmacológicas na perspectiva de atenuar ou prevenir os desfechos relacionados à tríade HIV, TARV e inflamação, o presente projeto pretende:(a) Investigar a presença de inflamação sistêmica e desfechos musculares e cerebrais, em PVHA, comparando diferentes faixas etárias;(b) Identificar a associação entre os desfechos acima e o padrão inflamatório da dieta, controlando por variáveis demográficas; nadir do CD4+; tempo e tipo de TARV; nível de atividade física e outras variáveis do estilo de vida.

Avaliação dos Riscos e Benefícios:
Conforme apresentado pela pesquisadora:
Riscos:
As avaliações realizadas neste estudo envolvem risco mínimo aos participantes, que estão descritas a seguir:A aplicação de questionários pode trazer algum desconforto ao avaliado ao ser questionado sobre hábitos de sua vida, especialmente os questionários sobre saúde mental, porém estas são avaliações utilizadas com frequência na prática clínica. A avaliação de sono pode

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trazer pequenos desconfortos físicos, uma vez que o participante deverá dormir uma noite com o aparelho para esta avaliação. Este desconforto é pequeno uma vez que se trata de duas fitas elásticas colocadas na cintura e uma cânula nasal para avaliação de sua respiração. A coleta de amostra de sangue pode trazer desconforto ao paciente por se tratar de um procedimento invasivo, podendo causar um pouco de dor no momento da coleta. A coleta de amostras de sangue com uma agulha inserida numa veia no braço é normalmente efetuada como parte dos cuidados médicos de rotina e pode causar um ligeiro desconforto. Algumas pessoas podem desmaiar durante ou após uma coleta de sangue. Por favor avise o profissional do estudo caso isso tenha ocorrido com você alguma vez. Raramente, a coleta de sangue pode causar dor, hematomas, sangramento ou inflamação no local da punção. Existe também uma pequena possibilidade de infecção. Para sua proteção, todos os procedimentos serão realizados por pessoas experientes, sob condições de higiene cuidadosas. A quantidade de sangue coletada em cada visita é pequena e insuficiente para causar anemia.

Benefícios:
Todos os resultados das avaliações serão informados aos participantes, após a conclusão do estudo. Serão ainda realizadas palestras informativas sobre alguns aspectos da coleta, por exemplo a qualidade da dieta. O estudo contribuirá para o melhor entendimento condições de saúde pessoas que vivem com o HIV, e também servirá para o planejamento de ações não farmacológicas (que não envolvem novos medicamentos) no futuro. Não há despesas pessoais para o participante em qualquer fase do estudo, incluindo exames e consultas. Também não há compensação financeira relacionada à sua participação (transporte, alimentação e/ou qualquer gasto que o(a) senhor(a) possa vir ater, será de responsabilidade totalmente sua).

Comentários e Considerações sobre a Pesquisa:
Pesquisa relevante.

Considerações sobre os Termos de apresentação obrigatória:
TCLE - Adequado;
Carta de anuência adequada e folha de rosto preenchida corretamente.

Conclusões ou Pendências e Lista de Inadequações:
Aprovado

Considerações Finais a critério do CEP:

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Continuação do Parecer: 3.100.321

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1159273.pdf	03/12/2018 21:15:37		Aceito
Outros	RESPOSTAS_PARECER.pdf	02/11/2018 15:32:48	Sandra Maria Lima Ribeiro	Aceito
Parecer Anterior	PB_PARECER_CONSUBSTANCIADO_CEP_2953556.pdf	02/11/2018 15:32:21	Sandra Maria Lima Ribeiro	Aceito
Outros	ANUENCIA.pdf	02/11/2018 15:32:10	Sandra Maria Lima Ribeiro	Aceito
Declaração de Manuseio Material Biológico / Biorepositório / Biobanco	TERMO_BIOBANCO.pdf	02/11/2018 14:53:55	Sandra Maria Lima Ribeiro	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_V2.pdf	02/11/2018 14:53:41	Sandra Maria Lima Ribeiro	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_REFEITO.pdf	02/11/2018 14:53:24	Sandra Maria Lima Ribeiro	Aceito
Folha de Rosto	folha_rosto_HIV.pdf	22/08/2018 10:28:26	Sandra Maria Lima Ribeiro	Aceito
Brochura Pesquisa	brochura_pesq.pdf	07/08/2018 12:59:12	Sandra Maria Lima Ribeiro	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 21 de Dezembro de 2018

Assinado por:
Kelly Polido Kaneshiro Olympio
(Coordenador(a))

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Telefone: (11)3061-7779 **Fax:** (11)3061-7779 **E-mail:** coep@fsp.usp.br

CURRÍCULO LATTES

Candidato – Marcus Vinicius Lucio dos Santos Quaresma

Marcus Vinicius Lucio dos Santos Quaresma

Endereço para acessar este CV: http://lattes.cnpq.br/3887289666580541

ID Lattes: **3887289666580541**

Última atualização do currículo em 12/04/2022

Possui graduação em Nutrição pelo Centro Universitário São Camilo (2013), atuou como estagiário no Centro de Estudos em Psicobiologia e Exercício (CEPE) no ano de 2013, foi aluno de treinamento técnico (TT3) na Universidade Federal de São Paulo no ano de 2014; Especializado em Fisiologia do Exercício Aplicada à Clínica (UNIFESP-BS) (2015) e Nutrição Esportiva: Bases fisiológicas, bioquímicas e moleculares (FAPES-SP) (2016). Especialista em Nutrição Esportiva pela Associação Brasileira de Nutrição (ASBRAN). Mestre em Ciências pela Universidade Federal de São Paulo (2017). Atualmente é aluno de Doutorado na Universidade de São Paulo (2018 - 2022) e Membro do Grupo de Estudos em Nutrição, Atividade Física e Processos de Envelhecimento (NAFE-USP). Docente do curso de Nutrição do Centro Universitário São Camilo. Foi nutricionista Clínico no Ambulatório de Nutrição do Setor de Lípides, Aterosclerose e Biologia Vascular (2014 - 2018). Atualmente é Nutricionista Esportivo do Clube de Atletismo Orcampi (2017 - Atual). Membro diretivo da Associação Brasileira de Nutrição Esportiva (2014 - Atual). Possui experiência com sono e distúrbios do sono, metabolismo lipídico, microbioma intestinal, inflamação sistêmica e desordens musculoesqueléticas. No doutorado estuda a prevalência de Sarcopenia em pessoas vivendo com o vírus da imunodeficiência (HIV). No Centro Universitário São Camilo, ministra as disciplinas de bases de nutrição humana, bioquímica, avaliação nutricional de adultos e idosos e nutrição em esportes. Como docente de pós-graduação na São Camilo-SP, UNIFESP-BS, UNIFESP-SP e CEFIT, ministra as disciplinas de nutrição esportiva, suplementação nutricional, tópicos em avaliação nutricional e metabolismo de lipídeos. **(Texto informado pelo autor)**

Identificação

Nome Marcus Vinicius Lucio dos Santos Quaresma

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2018 Doutorado em andamento em Saúde Pública (Conceito CAPES 6).
Universidade de São Paulo, USP, Brasil.
Título: Frequência de sarcopenia em pessoas vivendo com o vírus da imunodeficiência humana (HIV) e associação com a inflamação sistêmica e variáveis do estilo de vida,
Orientador: Sandra Maria Lima Ribeiro.
Palavras-chave: Envelhecimento; Sorodiagnóstico de HIV; Microbiota; Inflamação.

2015 - 2017 Mestrado em INTERDISCIPLINAR EM CIÊNCIAS DA SAÚDE (Conceito CAPES 5).
Universidade Federal de São Paulo, UNIFESP, Brasil.
Título: A Influência do débito de sono na fisiologia do tecido adiposo branco e marrom,Ano de Obtenção: 2017.
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Bolsista do(a): Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES, Brasil.

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2014 - 2015 Especialização em Fisiologia do Exercício Aplicada à Clínica. (Carga Horária: 360h).
Universidade Federal de São Paulo, UNIFESP, Brasil.
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2010 - 2013 Graduação em Nutrição.
Centro Universitário São Camilo, USC, Brasil.
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2005 - 2008 Ensino Médio (2º grau).
Escola Estadual Zenaide Lopes de Oliveira Godoy, E.E.Z.L.O.G, Brasil.

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Última ocorrência: Matrícula de Acompanhamento em 21/03/2022

Sigla	Nome da Disciplina	Início	Término	Carga Horária	Cred.	Freq.	Conc.	Exc.	Situação
HNT5770-1/3	Políticas Públicas de Alimentação e Nutrição	05/03/2018	17/06/2018	60	4	85	B	N	Concluída
MCM5880-4/1	Bioestatística I (Faculdade de Medicina - Universidade de São Paulo)	06/03/2018	30/04/2018	120	8	100	A	N	Concluída
MPR5730-6/2	Epidemiologia Clínica (Faculdade de Medicina - Universidade de São Paulo)	12/04/2018	20/06/2018	90	6	90	A	N	Concluída
MCM5712-6/2	Tópicos Avançados em Imunologia (Faculdade de Medicina - Universidade de São Paulo)	03/05/2018	11/07/2018	30	2	100	A	N	Concluída
HNT5737-4/1	Ciência de Alimentos	10/05/2018	21/06/2018	60	4	93	A	N	Concluída
ICB5752-1/4	Como Comunicar Sua Ciência: Melhorando a Oratória e a Empatia com o Público (Instituto de Ciências Biomédicas - Universidade de São Paulo)	25/06/2018	08/07/2018	30	0	-	-	N	Pré-matrícula indeferida
ICB5747-2/3	Ciências Ômicas em Doenças Infecciosas (CODI) (Instituto de Ciências Biomédicas - Universidade de São Paulo)	02/07/2018	22/07/2018	90	0	-	-	N	Matrícula cancelada
HNT5773-1/1	Fragilidade no Idoso: Prevenção e Intervenções	11/09/2018	24/09/2018	60	4	90	A	N	Concluída

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Sigla	Nome da Disciplina	Início	Término	Carga Horária	Cred.	Freq.	Conc.	Exc.	Situação
	Relacionadas à Nutrição e Atividade Física								
HNT5776-1/1	Projetos de Pesquisa em Alimentação e Nutrição: Concepção e Planejamento	03/05/2019	11/07/2019	60	4	75	A	N	Concluída
PSP5110-2/1	Saúde Pública e Envelhecimento	12/03/2020	28/05/2020	60	4	100	A	N	Concluída
MIP5734-4/2	Pesquisa Aplicada à Infecção por HIV/Aids: Abordagens, Métodos e Técnicas (Faculdade de Medicina - Universidade de São Paulo)	26/05/2020	29/06/2020	75	0	-	-	N	Turma cancelada
ICB5776-1/1	Imunologia Sistêmica (Instituto de Ciências Biomédicas - Universidade de São Paulo)	03/11/2020	04/12/2020	60	0	-	-	N	Matrícula cancelada

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Orientador: Julio Orlando Tirapegui Toledo.
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Setores de atividade: Nutrição e Alimentação; Saúde Humana.

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Artigos científicos e capítulos de livros produzidos em colaboração ao longo do doutorado

Artigo 1 – The dietary inflammatory index (DII®) and its association with cognition, frailty, and risk of disabilities in older adults: A systematic review – Publicado Clinical Nutrition ESPEN (Clin Nutr ESPEN. 2020 Dec;40:7-16.)

Artigo 2 – Dietary patterns and sleep quality in young adults: a systematic review. Submetido à revista Sleep Health e negado. Atualmente está em ajuste para nova submissão.

Artigo 3 – Covid-19 social distancing, lifestyle and health outcomes among Persons living with HIV (PLWH): a web-based survey – Aceito para publicação AIDS and Behavior

Artigo 4 - Association between sleep quality and lifestyle factors in persons living with HIV during the COVID-19 social distancing: a web-based survey. Submetido à revista Sleep Health e negado. Atualmente está em ajuste para nova submissão.

Capítulo de Livro – Modificações da Microbiota Intestinal e Associação com Inflamação Sistêmica do Envelhecimento. Publicado – Programa de Atualização em Nutrição Clínica: Ciclo 10 / Organizado pela Associação Brasileira de Nutrição.

Artigo 1 – The dietary inflammatory index (DII®) and its association with cognition, frailty, and risk of disabilities in older adults: A systematic review – Publicado na Clinical Nutrition ESPEN (Clin Nutr ESPEN. 2020 Dec;40:7-16.)

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Narrative Review

The dietary inflammatory index (DII®) and its association with cognition, frailty, and risk of disabilities in older adults: A systematic review

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SUMMARY

Background & aims: Systemic inflammation is considered an important issue in older adults and is associated with adverse health outcomes, such as frailty and cognitive impairment. Diet is a critical associated factor, and the dietary inflammatory index (DII®) is proposed as a promising tool to identify the association between diet and health outcomes. Our aims were: (i) to investigate the association between the DII® and frailty, cognition, and the consequent risk of disability in older adults; (ii) to discuss particularities of the use of DII® with older adults.

Methods: The research question was based on the PICOS strategy: Population = older adults; Intervention or Exposure = DII; Comparison = any comparator; Outcomes = frailty, cognition, and risk of disability; Type of study = cohort, cross-sectional or case–control studies. We searched publications in two electronic databases (PUBMED and Web of Science) up to May 20th, 2020.

Results: Seven studies met our criteria. Three investigated cognition (one cohort and two cross-sectional), and four investigated frailty or risk of disability (one cohort and three cross-sectional); none of the studies investigated both outcomes (frailty and cognition) simultaneously. The studies presented some issues, mainly concerning: (i) the collection of dietary data and calculation of the DII; (ii) the study design; (iii) calculation of the sample size; (iv) eligibility criteria; (v) time for follow-up; (vi) and choice of covariates.

Conclusion: despite the issues, the use of DII resulted in a significant association, or predictive value, with variables related to frailty and cognitive decline. Further studies, with sensitivity analysis of the different components of this index, are needed. DII showed to be a promising tool in the investigation of geriatric syndromes. This systematic review was registered in PROSPERO (CRD42020155672).

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1. Introduction

Aging is a stage of life marked by interrelated changes, including body composition, deficits in energy metabolism, homeostatic dysregulation, and neurodegeneration. These changes are recognized as the reduced capacity of dealing with biological, environmental, and psychological stressors, leading ultimately to physical and cognitive decline [1,2].

The process of aging appears to reduce some meaningful connections between brain and muscle. Studies performed in older adults have shown low concurrent performance on cognitive tests and grip strength [3–6]. Miyamura et al. [7], in a systematic review, searched studies associating frailty syndrome and cognitive impairment in older adults and found most studies pointing frailty as a trigger for cognitive decline. These concurrent processes in brain and muscle have been highlighted in the construction of

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important concepts related to aging, such as cognitive frailty, intrinsic capacity, motoric cognitive risk, among others [8–11].

Therefore, the early identification of factors associated with both conditions can contribute to the timely planning of intervention strategies. One important associated and maybe causal factor is a picture of low-grade systemic inflammation, which Franceschi et al. [12] name *inflammaging*. This concept was coined based on significant immune changes linked to aging. In fact, as part of the immunosenescence, all the immune system's functions suffer a reshaping both at the innate and adaptative arms [13–15], and the concept of *inflammaging* highlights the macrophage's senescence. These cells become hyperfunctioning, secreting, as a consequence, a disproportional number of inflammatory cytokines. Also, recent hypotheses point the development of *inflammaging* as occurring elsewhere in the body, in addition to the immune system [16]; organs with immunometabolic activity, for instance, adipose tissue and gut, are mainly involved in these processes [16].

The increase and redistribution of body fat related to aging result in augmented visceral adipose tissue (VAT) [17,18]. The high-fat content VAT becomes a target of macrophages and T lymphocytes infiltration, which elevates the secretion of the pro-inflammatory cytokines [19], and imbalances the production of adipocytokines [17,18,20]. The liver is also involved in this pro-inflammatory status, producing C-reactive protein (CRP) in response mainly to IL-6 [19].

Concerning the gut, it is observed, with aging, changes in the profile of the commensal microbiota, resulting in an abnormal activation and reduced tolerance of the gut-associated lymphoid tissue (GALT). These aspects lead to adverse modifications of the barrier function of the intestine; consequently, the gut becomes permeable ("leaky gut"), allowing translocation of bacteria and bacterial fragments such as lipopolysaccharide (LPS) [21,22]. The LPS, in turn, enters the capillaries and further binds to specific pattern recognition receptors in different tissues (for instance, adipose, muscular, liver, pancreas, among others), activating pathways related to inflammation [23].

Finally, aging reduces the homeostatic control of stress, oxidation-inflammation, cytokines production, DNA repair, autophagy, and others; molecules and metabolites derived from these processes are now recognized as antigens, activating different inflammatory pathways, all these events contributing with the increased inflammatory status [16,24].

Therefore, *inflammaging* is a process derived from several age-related body changes and has been a plausible explanation for different adverse outcomes. For instance, in skeletal muscle, inflammatory cytokines might reduce protein synthesis, increase protein degradation, which in turn can result in lower muscle mass, increased risk of physical frailty, and ultimately, incapacities [9,25,26]. Besides, some inflammatory molecules can cross the blood–brain barrier modulating neuroinflammation and, consequently, compromising functions such as cognition [27,28].

Nutrition, as part of modifiable lifestyle factors, can be considered an essential approach in managing *inflammaging*. Diet and its components have shown the potential to modulate the inflammatory status in muscle, brain, and many other tissues [29–35]. Thus, the choice of appropriate methods to investigate and interpret dietary intake is fundamental.

In general, dietary intake can be investigated from indices, or scores, composed of multiple dietary factors, providing a comprehensive way to interpret the associations between diet and different outcomes. Cavicchia et al. [36], and posteriorly Shivappa et al. [37] proposed a score named dietary inflammatory index (DII®). The current version of DII suggests a list of 45 items composed by energy, nutrients (carbohydrates, protein, total fat, saturated, monounsaturated, polyunsaturated, omega-3 and omega-6 fatty acids, trans fat, vitamins A, C, D, E, B6 and B12, niacin, riboflavin, β-carotene, folic acid, iron, cholesterol, magnesium, selenium, thiamin, zinc), food components (alcohol, caffeine, fiber, eugenol, flavan-3-ol, flavanones, flavones, flavanol, anthocyanins, and isoflavones), foods and spices (garlic, ginger, onion, saffron, green or black tea, oregano, turmeric, pepper, and rosemary). All these components were selected from a systematic review, and presented significant associations with some biomarkers of inflammation [37]. This index had their interpretability improved with the adjustment of the centered percentile of each component, based on databases of dietary intake of different countries [37]. The higher scores of the DII indicate a more pro-inflammatory diet, while the lower scores mean a more anti-inflammatory diet. Since the publication of DII in 2014, several studies with different populations and age intervals have investigated the association between this index and various health outcomes [38–42]. Here, we intend to identify studies investigating the association of DII® with cognition and frailty in older adults.

As such, the framework of our hypothesis was the following: (i) Frailty and cognitive impairment are important issues related to aging; (ii) Both outcomes (frailty and cognition) seems to occur interrelated; (iii) One physiological connector between frailty and cognition seems to be a low-grade inflammatory status, typical of aging (called inflammaging); (iv) nutrition may be an essential modulator of *inflammaging*, and consequently on the development of frailty and cognitive decline; (v) The DII® is proposed to be a sensitive index to identify the inflammatory potential of the diet, and its use in older adults deserve specific discussions. As such, this manuscript aimed to answer, from a systematic review, the question: *Is the DII® associated with frailty, cognition, and the consequent risk of disabilities in older adults?* Secondarily, we intended to discuss aspects related to the use of DII in studies with older adults.

2. Materials and methods

We performed a systematic review of the literature following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses- PRISMA [43]. This protocol is registered in PROSPERO (CRD42020155672). The research question was based on the PI(E)COS formulation, as following: Population = older adults at baseline; Intervention or Exposure = Dietary Inflammatory Index (DII); Comparison = any; Outcomes = frailty, cognition, and risk of disability; Type of study = cohort, cross-sectional or case–control studies.

2.1. Search strategies

Databases searched were PUBMED and Web of Science. From PUBMED the search was performed with the descriptors indicated by Medical Subject Headings (Mesh) and boolean operators "OR" and "AND", as following: (((((“Aged" [Mesh]) OR "Frail Elderly" [Mesh]) OR "Aged, 80 and over" [Mesh] OR "Elderly" OR "Older Adults") AND "Frailty" [Mesh]) OR ("Cognition" [Mesh] OR "Cognition Disorders" [Mesh] OR "Sarcopenia" OR "Disability*") AND "dietary inflammatory index"). In the Web of Science database, the search combinations were: (("dietary inflammatory index") AND ("older adults" OR "elderly" OR "aged" OR "older") AND ("cognitive" OR "cognitive impairment" OR "frailty" OR "sarcopenia" OR "disability*")). The search included publications up to May 20th, 2020, without any additional time restriction.

2.2. Detailed inclusion and exclusion criteria

To be included, the studies had to: -Be performed with older adults (60 ≥ years old at baseline); -To investigate one or more of the

following outcomes: frailty, sarcopenia, cognitive impairment and risk of disabilities; -be featured as epidemiological (cohort, cross-sectional or case–control). We excluded the literature reviews, *in vitro* or non-human studies, studies that adopted the first version of DII or other dietary index different from Shivappa's proposal [37].

Our systematic review was developed according to the following steps:

1st step. Reading of the titles and abstracts to exclude the ones not related to the research question, as well as the duplicates. This 1st step was initially performed by the first and second authors (BMV and MVLSQ) and checked by the fourth author (SMLR). The divergences of this step were solved by a consensus meeting.

2nd step. Acquisition of the selected articles in full and perusal to identify in detail the inclusion and exclusion criteria. This step was performed by two authors independently (BMV and CMM), and the divergences were solved together with the fourth author (SMLR) by a consensus meeting.

3rd step. Data extraction of the studies by the first author (BMV), checked by the second author (MVLSQ) and organized in an Excel® 2013 file. The information extracted were: authors, title, year and local of publication, study design, number of participants as well as their sex and age; objectives of the study, type of outcome and methods of investigation of these outcomes; methods of food intake evaluation and components adopted to calculate the DII, and covariables investigated.

2.3. Quality assessment and limitations of the studies

The quality of the studies was assessed independently by the first and second authors (BMV and MVLSQ), using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Institutes of Health (NIH) [44] (Supplementary Table S1). Besides, we checked the compliance of each study with the checklist of the Strengthening the reporting of observational studies in epidemiology (STROBE) statement [45] (Supplementary Table S2). In addition, considering the etiological complexity of the outcomes (frailty and cognition) and the exposition (DII) of our systematic review, we included in the qualitative analysis of the studies: (i) The type and number of the covariables included in each study; (ii) The steps and procedures followed to calculate the DII. The divergences between these assessments by the authors were solved by a consensus meeting.

3. Results

Searches in both databases resulted in 40 articles, from which 13 were excluded as duplicates, and 12 were excluded for not attending our research question. Therefore, 15 studies were eligible to be read in full. In this step, 8 studies were excluded because they did not meet the established criteria, and seven studies were included and had their data extracted (Fig. 1).

3.1. Summary of findings

Table 1 shows the general characteristics of the articles. The totality was published in English; four of them were held in North America [46–49], two in the Asian continent [50,51], and one in Europe [52]. All the studies were published from 2017 to 2019. Three studies investigated the association between DII and cognitive decline, memory, and dementia risk [46,47,51] and four publications investigated the association between DII and frailty, pre-frailty, and risk of disabilities [48–50,52]. Two studies were cohorts [46,52] and five were cross-sectional [47–51]. The two cohorts and three of the cross-sectional studies [47–49] were secondary analysis from broader studies; three were derived from the National Health and Nutrition Examination Survey (NHANES – EUA) [47–49], one from a Spanish cohort study Seniors-ENRICA [52], and one from the United States of America randomized clinical trial The Women's Health Initiative Memory Study (WHIMS) [46]. The other studies adopted convenience samples from Health Centers [50,51]. All the studies were performed with community-dwelling older adults with 60 or more years old at baseline, and sample sizes varied from 239 to 7182. Two studies investigated the same sample [48,49]. The articles included participants of both genders, except for one [46], which included only women, [46], from the WHIMS (n = 7085). Lohman et al. [48] used aggregated data from NHANES (from 2007 to 2014), including only participants older adults with complete data on obesity, diet, and frailty measures for analysis (n = 7182). In turn, Frith et al. [47] used data of persons from 65 to 85 years old from NHANES waves 2011–2012 and 2012–2013, and excluded persons with one or more of the following chronic diseases: congestive heart failure, coronary artery disease, heart attack, stroke or physician-diagnosed diabetes (n = 1723).

The methods adopted to evaluate the food intake (a necessary step to calculate the DII) were 24-h dietary recall (24HR) [47–51], food frequency questionnaires (FFQ) [46], and electronic diet history [52]. Concerning differences in DII calculation between the studies, four of them used a variation of the index based on the adjustment by 1000 kcal energy [47–49,51]. The number of food components of DII varied from 20 to 33, out of the 45 possible. Three studies [46,50,52] included foods and spices from the DII list of components (ginger, turmeric, pepper [50], onion [50,52], green/black tea [46,50,52] and garlic [52]); four studies used only the nutrients or food components from DII parameters list. Regarding the score of DII, from the four studies performed in the USA, one of them did not give any information about the score or the quartile range [49]. From the other three, two of them [46,52] showed values ranging between −5.0 and + 5.0 using 32 [46] and 27 [52] parameters, and one of them [47] showed lower ranges (about −3.0 to 3.0) using 26 parameters. The two studies performed in South Korea showed different ranges for the DII. Kim & Park [50] found the DII ranging from about −2,5 to +4.0 using 33 parameters, and Shin et al. [51] presented the DII ranging from −1.0 to +1.0 using 20 parameters. The study performed in Spain [52], identified the DII between about −0.7 and +2.0 using 32 parameters.

The frail identification was performed using the five criteria proposed by Fried et al. by two studies [50,52], and two studies used only four of those criteria, which was validated in NHANES [48,49]. Laclaustra et al. [40] investigated risk of disabilities using daily activities and daily instrumental activities questionnaires [53]. The studies that investigated cognition as outcome [46,47,51] used diverse methods. Hayden et al. [46] examined the cognitive function by a neuropsychological battery [54], and Frith et al. [47] applied three memory tests (CERAD - Consortium to Establish a Registry for Alzheimer's Disease; DSST - Digit Symbol Substitution Test, and Animal Fluency Test). Shin et al. [51], in turn, used a Korean adapted version of the Mini Mental State Examination (MMSE), the K-MMSE.

Table 2 shows the main results of the studies. The publications using frailty as the outcome, overall showed that the higher the DII (and therefore, the more inflammatory diet), the higher the odds of being frail or pre-frail [48–50]. The DII was also able to predict frail, as well as the risk of disabilities, in about three years follow-up [52]. Three studies investigated cognition as the outcome [46,47,51]. The results from the two cross-sectional studies [47,51] showed the higher DII to be associated with cognitive decline, poor memory, and increased risk of dementia. The ten years follow up investigated by Hayden et al. [46] pointed the DII as a predictor for incident dementia.

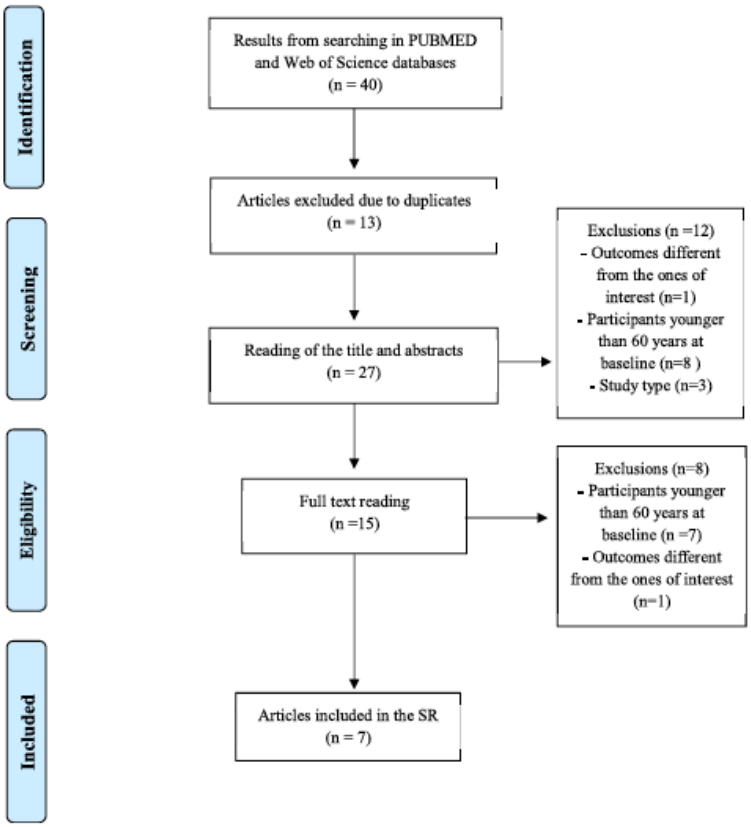

Fig. 1. Flow-chart of studies selection. Adapted from PRISMA.

Regarding covariables, the totality of the studies with frailty as the outcome included age, sex, education, and presence of one or more chronic diseases [48–50,52]. Three studies included smoking [48,49,52], and two evaluated race/ethnicity [48,49]; Kim & Park [50] added chewing ability and energy intake, and Laclaustra et al. [52] included the body mass index (BMI). Only Laclaustra et al. [52] evaluated the time spent watching TV, leisure-time physical activity, and the adherence to the Mediterranean Diet (MEDAS). Lohman et al. [48] was the only study that included economic conditions (household income-to-poverty ratio), and marital status.

As leading associations with the covariables, the frail participants were older than the pre-frail or the robust ones [48–50]; the participants who were frail and with more inflammatory diets were the ones with lower education level, lesser physical activity levels, reduced BMI, and lower energy intake [48,49]. Kim & Park [50] used the Mini-Nutritional Assessment (MNA) and identified that the participants with the most impoverished nutritional status were also the frailest and the ones with the most inflammatory diets. Lohman et al. [48] showed that the inflammatory potential of the diet and obesity were independently and positively associated with being frail.

The studies with cognition as the outcome [46,47,51] had as common covariables the age, the BMI, and investigation of physical activity [46,47,51]. The sex, race/ethnicity, and sleeping aspects were shared between two studies [47,51]; Hayden et al. [46] and Shin et al. [51] included education; Hayden et al. [46] and Frith et al. [47] included smoking habit. Besides, one study [46] included the use of hormone therapy, presence of diabetes, hypertension, medications to hypercholesterolemia, nonsteroidal anti-inflammatory drug (NSAID) use, energy intake, and geographic region. Frith et al. [47] also included depressive symptoms, and Shin et al. [51] included the use of nutritional supplements, self-reported health conditions, and a history of dementia. As the main results, the higher scores of DII were associated with lower levels of physical activity, less formal education, and older age [46,47,51].

Overall, the covariables common to both outcomes (but not included in all the studies) were age, sex, BMI, physical activity, race, ethnicity, education, different chronic diseases, and smoking. Important to notice that none of the studies with cognition as the outcome included frailty as covariable, and likewise, none of the studies investigating frailty included cognition as a covariable.

3.2. Quality assessment and limitations of the studies

The quality checklist of the NIH tool, considering a critical analysis, showed the totality of the studies within a range varying from "Fair" to "Good", being the study of Hayden et al. [46] the best quality and Kim & Park [50] the fairest (Supplementary Table 1 and Fig. 2). Additionally, the compliance with the STROBE checklist [45]

Table 1
Main features of the studies included (n = 7).

Author, year	Country	Aims	Study design	Sample size, age and sex	Dietary assessment method and number of DII food parameters out of 45.	Outcomes and measurements
Hayden et al., 2017 [46]	United States	To evaluate the associations between DII, global cognition and incident mild cognitive impairment or probable dementia in older women.	Cohort (10 years follow-up)	7085 65–79 years old F	WHI-FFQ 32 food parameters: vitamin B12, B6, A, C, D, E, β-carotene, caffeine, carbohydrate, cholesterol, energy, total fat, fiber, folic acid, iron, magnesium, monounsaturated fatty acids, niacin, omega 3, omega 6, onion, protein, polyunsaturated fatty acids, riboflavin, saturated fat, selenium, thiamin, trans fat, zinc, green/black tea, isoflavones.	Cognitive impairment, incident cognitive impairment and dementia Neuropsychological test by certified technicians: 3MS (primary screening), CERAD, Trail Making Test parts A and B, PRIME-MD, GDS-short (15-item), interview.
Frith et al., 2018 [47]	United States	To examine the association between DII and memory functions.	Cross- sectional	1723 60–85 years old M/F	24-h dietary recall 26 food parameters[a]: carbohydrate, protein, fat, alcohol, fiber, cholesterol, saturated, monounsaturated, and polyunsaturated fatty acids, niacin, thiamin, riboflavin, vitamin B12, B6, A, C, D, E, Fe, Mg, Zn, Se, folic acid, β-carotene, omega 6 and omega 3.	Cognition and memory function (episodic, semantic, and working) Episodic memory: CERAD - three learning trials and a delay trial. (maximum score for each trial = 10). Semantic memory: Animal Fluency – nomination of as many animals as possible in 1 min (one point for each named animal). Working memory: DSST - numbers paired with symbols (maximum score is 133).
Kim & Park, 2018 [50]	South Korea	To examine whether DII was positively associated with the risk of frailty in older adults, based on the nutritional status.	Cross-sectional	321 70–85 years old M/F	24-h dietary recall 33 food parameters: carbohydrate, fat, protein, fiber, vitamin A, D, E, C, B6, B12, β-carotene, thiamin, riboflavin, niacin, folate, magnesium, iron, zinc, selenium, omega 3, omega 6, cholesterol, saturated, monounsaturated, and polyunsaturated fatty acids, garlic, ginger, onion, turmeric, green/black tea, pepper, alcohol, and caffeine.	Frailty and nutritional status Frailty: Fried phenotype [frail (3 or more criteria), pre-frail (one or 2 criteria), and non-frail (not meet any of criteria)] Nutritional status: MNA [good nutritional status (>24), risk of malnutrition (17–23.5), malnutrition (<17)]. Poor nutritional status included both (risk of malnutrition and malnutrition).
Shin et al., 2018 [51]	South Korea	To investigate the association between DII and cognitive function in older persons.	Cross-sectional	239 ≥65 years M/F	24-h dietary recall 20 food parameters[a]: energy, carbohydrates, fat, protein, vitamins A, B1, B2, B3, B6, B12, C, E, saturated, monounsaturated, and polyunsaturated fatty acids, fiber, cholesterol, iron, zinc, and folic acid.	Cognitive function K-MMSE – 19 items and score ranging from 0 to 30 [normal (25–30), boundary zone (20–24), mild cognitive impairment (15–19), and moderate cognitive impairment (10–14)].
Laclaustra et al., 2019 [52]	Spain	To examine the association between DII and frailty and disability.	Cohort (2–4 years follow-up)	1948 ≥60 years old M/F	Diet History 32 food parameters: carbohydrate, protein, fat, alcohol, vitamin B12, B6, A, C, D, E, thiamin, riboflavin, niacin, β-carotene, caffeine, cholesterol, total fat, saturated fatty acids, monounsaturated, polyunsaturated fatty acids, trans fat, energy, fiber, folic acid, iron, magnesium, omega 6, and omega 3, Se, Zn, green/black tea, onion, and garlic.	Frailty, reduced physical performance, and disability Frailty: Fried phenotype [frail (3 criteria)]. Reduced physical performance: SPPB – 3 components test; score range 0–12 [functional limitation (≤9)]. Disability: Lawton and Brody scale IADL (a reported difficulty in any of the items classified the participant as having disability).
Lohman et al., 2019 [48]	United States	To investigate associations between obesity, DII and frailty among older adults.	Cross-sectional	7182 ≥60 years old M/F	24-h dietary recall 27 food parameters[a]: carbohydrates, protein, fat, alcohol, fiber, cholesterol, saturated, monounsaturated, and polyunsaturated fatty acids, omega 3, omega 6, niacin,	Frailty and obesity Frailty: 4 modified criteria [frail (3 or 4 criteria), pre-frail (1 or 2 criteria), and robust (any criteria)]. Obesity: BMI (obesity ≥ 30 kg/m^2).

(continued on next page)

Table 1 (*continued*)

Author, year	Country	Aims	Study design	Sample size, age and sex	Dietary assessment method and number of DII food parameters out of 45.	Outcomes and measurements
					vitamins A, B1, B2, B6, B12, C, D, E; iron; magnesium; zinc, selenium, folic acid, β-carotene, and caffeine.	
Resciniti et al., 2019 [49]	United States	To investigate the association between DII, pre-frailty and frailty among older US adults	Cross-sectional	7182 ≥60 years old M/F	24-h dietary recall 26 food parameters[a]: carbohydrate, protein, fat, alcohol, fiber, cholesterol, saturated fatty acids, monosaturated, polyunsaturated fatty acids, niacin, thiamin, riboflavin, vitamin B12, B6, A, C, D, E, Fe, Mg, Zn, Se, folic acid, β-carotene, omega 6, and omega 3.	Pre-frailty and frailty Frailty: 4 modified criteria [frail (3 or 4 criteria), pre-frail (1 or 2 criteria), and robust (any criteria)].

3MS, Modified Mini–Mental State Examination, BMI, Body Mass Index; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DII; Dietary Inflammatory Index; DSST, Digit Symbol Substitution Test; F, Female; FFQ, Food Frequency Questionnaire; GDS-short, Geriatric Depression Scale-short; IADL, Instrumental Activities of Daily Living; K-MMSE, Korean version of MMSE; M, Male; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; PRIMED-MD, Primary Care Evaluation of Mental Disorders Patient Questionnaire; SPPB, Short Physical Performance Battery; Women's Health Initiative - Food Frequency Questionnaire.

[a] Energy-adjusted DII scores were calculated by dividing the food parameters by energy intake and then multiplying by 1000.

Table 2
Main results of the studies included (n = 7).

Author, year	Statistical analysis	Main results	Covariates/adjustment variables
Hayden et al., 2017 [46]	Mixed models adjusted for baseline covariables. Trajectory of cognitive impairment analyzed using Cox proportional hazard models, adjusted for baseline covariables.	The highest DII scores were associated with worse cognitive function and increased risk MCI and probable dementia (HR = 1.27; 95% CI: 1.06, 1.52).	Age, education, race, and hormone therapy, diabetes, hypertension, medications to hypercholesterolemia, NSAID use, BMI, physical activity, energy intake, geographic region, and smoking.
Frith et al., 2018 [47]	Multivariable linear regression	Higher DII scores were associated with worse in all memory parameters: episodic: ($b_{adjusted}$ = −0.39; 95% CI: −0.79, 0.00); working ($b_{adjusted}$ = −2.80; 95% CI: −5.58, −0.02); semantic: ($b_{adjusted}$ = − 1.18; 95% CI: −2.17, −0.20).	Age, sex, race-ethnicity, BMI, smoking status, hours of sleep per night, leisure-time moderate-to-vigorous physical activity (min/week), and depression symptomatology (PHQ-9).
Shin et al., 2018 [51]	Linear and multiple logistic regression	DII was inversely associated with K-MMSE (β = - 0.58; 95% CI: - 1.11, - 0.06). The highest DII tercile had increased odds of MCI (OR = 6.32; 95% CI: 1.18, 33.78).	Sex, age, BMI, sleep hours, supplemental use, education level, self-reported health conditions, history of dementia, and physical activity.
Kim e Park, 2018 [50]	Multinomial logistic regression	Higher DII scores were associated with risk of frailty with poor nutritional status (OR = 1.68; 95% CI: 1.21, 2.34) but not in those with good nutritional status.	Age, chewing ability, and energy intake
Laclaustra et al., 2019 [52]	Logistic regression	Higher DII scores at baseline was associated with increased risk of frailty (OR = 2.48; 95% CI: 1.42, 4.44), disability (OR = 1.96; 95% CI: 1.03, 3.86), and reduced physical performance (OR = 1.22; 95% CI: 0.92, 1.62, not significant) at follow-up.	Age, sex, education, smoking status, BMI, diagnosed diseases, time spent watching TV, and leisure-time physical activity and MEDAS
Lohman et al., 2019 [48]	Logistic regression	The highest DII quintile presented higher likelihood to be frail (OR = 1.68; 95% CI: 1.10, 2.58). Also, obese individuals were more likely to be frail (OR = 2.24; 95% CI: 1.68, 2.99).	Age, sex, smoking status, race/ethnicity, education, household income-to-poverty ratio, and marital status, presence of ten common health conditions, including diabetes, arthritis, congestive heart failure, coronary heart disease, myocardial infarction, stroke, cancer, hypertension, osteoporosis, and kidney failure.
Resciniti et al., 2019 [49]	Multinomial logistic regression	The highest DII scores presented increased likelihood to be pre-frail (OR = 1.71; 95% CI: 1.36, 2.15) and to be frail (OR = 1.70; 95% CI: 1.02, 2.85).	Age, sex, race and ethnicity, education, smoking status, and summed score of 10 common comorbidities (arthritis, cancer, congestive heart failure, coronary heart disease, diabetes, heart attack, high blood pressure, osteoporosis, stroke, and weak or failing kidneys)

NOTE: all analysis results presented here are from adjusted models for the variables listed. BMI, Body Mass Index; CI, Confidence Interval; DII; Dietary Inflammatory Index; EDII, Empirical Dietary Inflammatory Index; HR, Hazard Ratio; K-MMSE Korean version of MMSE; MCI, mild cognitive impairment; MEDAS, Mediterranean Diet Adherence Score; MMSE, Mini Mental State Examinations; MNA, Mini Nutritional Assessment; NSAID, Non-Steroidal Anti-Inflammatory Drugs; OR, Odds Ratio; PHQ-9, Patient Health Questionnaire; SPPB, Short Physical Performance Battery.

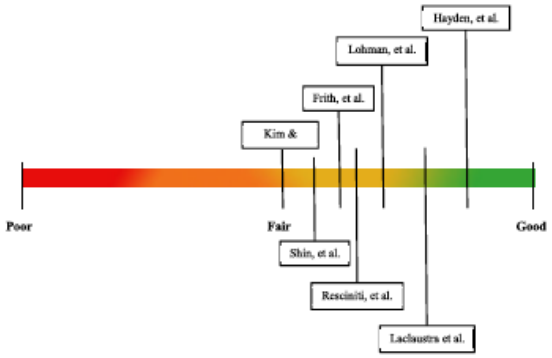

Fig. 2. Overall quality rating of observational cohort and cross-sectional included studies (n = 7). Assessment by NIH Assessment Tool for Observational Cohort and Cross-Sectional Studies, and the compliance of the studies with the STROBE checklist.

showed that only one study [52] fulfilled more than 75% of the items that make up the checklist, and the others accomplished between 50 and 75% [46–51] (Supplementary Table 2). According to the main issues derived from STROBE, none of the studies described the sample size related explicitly to the article. Instead, three studies [47–49] performed secondary analysis from broader studies, which in turn used representative samples. Regarding the eligibility criteria, the articles that used secondary data [46–49,52] considered the same eligibility criteria of the primary studies. Besides, two studies with primary data [50,51] presented the eligibility criteria incompletely, omitting to clarify about missing data.

4. Discussion

Our systematic review aimed to answer the question: *Is the DII® associated with frailty, cognition, and the consequent risk of disabilities in older adults?* Additionally, we aimed to identify some easiness and difficulties encountered by different studies in the use of DII with older adults and to discuss the needs for adaptations. Seven studies fulfilled our inclusion and exclusion criteria, three of them investigated cognition (one cohort and two-cross sectional), and four had frailty or risk of disabilities as outcomes (one cohort and three cross-sectional). None of the studies performed the investigation of both results (frailty and cognition) simultaneously. The studies showed qualities ranging from fair to good, with small issues related to sample size calculation, eligibility criteria, and methods of diet analysis. Apart from these issues, the use of the DII resulted in a significant association or predictive value of DII regarding frailty and cognitive decline.

4.1. Rationale for our hypothesis

We choose to put together frailty and cognition, based on different studies showing the concurrent occurrence of both conditions. While the frailty phenotype in general focus in physical domains (unintentional weight loss, self-reported exhaustion, slowness of gait speed, reduced handgrip strength, and physical inactivity), some authors include a more multidimensional point of view, with participation of cognitive and psychological deficits [54–57]. According to this broader standpoint, limitations in social or psychological resources accelerates the deterioration of both physical and cognitive functions [58]. Physical frailty and cognition are essential issues of aging, and studies have shown that the presence of one increases the risk of the development of the other [7,9].

Many external and internal factors seem to increase the risk of developing both frailty and cognitive decline. Some examples are genetic aspects such as polymorphisms of the APOE4, or of other genes involved in apoptotic and transcription regulation pathways [59]; social factors including low education, poor housing and low wages [60]; aspects of lifestyle such as low physical activity, smoking, alcohol abuse, and unhealthy dietary patterns [60]. All these factors can impair the maintenance of a healthy brain and open windows to frailty [9,61].

The overlapping mechanisms related to cognition and frailty certainly have the *inflammaging* as a connector [12,25,62]. Aging leads to an imbalance between the pro- and anti-inflammatory responses, shifting to a low-grade pro-inflammatory frame, which is also called *inflammaging* [25,26,62–64]. The inflammatory status increases oxidative stress and insulin resistance, which consequently reduces the muscle capacity to synthesize proteins [65]. The inflammatory molecules also can cross the blood–brain barrier elevating the neuroinflammation [66]. Neuroinflammation, in turn, reduces or modifies neurotransmitters and neurotrophic factors such as the brain-derived (BDNF) [66,67] favors the accumulation of undesirable molecules [25,62] such as mitochondrial DNA (mtDNA) [68], beta-amyloid and tau-protein [69] and compromises the brain communication with muscle. Thus, inadequate quantity and quality of muscle mass, increased by frailty, negatively affect the brain functioning [65].

Despite these promisor hypotheses that put together frailty and cognition, the studies included in our systematic review did not mention these connections, neither included one or other as covariables in the data analysis.

4.2. Frailty and cognitive decline in the context of nutrition and DII

Dietary intake modulates, positively or negatively, the bodily inflammatory status [29–35,70]. For instance, excessive energy intake can result in high body fat, creating inflammatory deposits (adipose tissue), which secret inflammatory adipokines, and aggregate immune cells [71]. In turn, some nutrients can directly modulate the expression of molecules involved in inflammatory pathways. For example, saturated fatty acids can increase the phosphorylation of MAPKs, enhancing the activation of transcription factors such as nuclear factor (NF)-κB and elevating the expression of inflammatory genes [72]. On the other side, phenolic compounds could suppress neuroinflammatory processes and neuronal apoptosis by inhibiting free radicals and cytokine production in microglia [73].

Identifying the benefits of different dietary compounds, Shivappa et al. [37] developed the DII. According to these authors, the advantage of this index is that it was developed based on evidence of an association between inflammation, nutrients, and food components. For these reasons, the authors consider the DII to be more robust and more sensitive to the small effects of some food components, compared to indices that consider only foods or food groups. One of the objectives of our systematic review was to identify some easinesses and difficulties in the use of DII with older adults and to discuss the need for adaptations.

Overall, the DII score ranged widely between the studies, although many of the publications did not clearly show these scores. The widest range was from about −5.0 to 5.0, in studies performed in the USA; still in the USA, the study with the shortest range [47] excluded, from the analytical sample, individuals with various chronic diseases, which can justify this different range in the same country. Importantly, from the components of DII in the USA studies, only one of them [46] included some of the food,

spices, or polyphenol in the calculation. Hayden et al. [46] included green/black tea and mentioned in their discussion that the lack of some components could underestimate the inflammatory pattern of the diet, but at the same time, they affirmed that the intake of that missed parameters is minimum in their country. The two studies performed in South Korea used small analytical samples and showed different ranges of DII between both studies from the same country. Maybe the sample sizes could bias the DII calculation and range. Regarding the DII components, Kim & Park [50] included ginger, onion, turmeric, green/black tea, and pepper. The only study performed in Europe (Spain) [52] showed the smallest range for the DII score, which included 32 components, with some food and spices (green/black tea, onion, and garlic).

Therefore, the number and type of components included in the DII calculation need a careful discussion; the absence of a clear presentation of the DII intervals makes it difficult to draw consistent conclusions. Essential aspects of diets may have been missed, and only three studies [46,47,50] discussed these absences as bias in the association analysis. Although the authors of DII [37] mentioned, in their publication, different tests and scenarios to investigate different parameters in the DII analysis, they did not carry out any sensitivity analysis to reinforce these statements. Further studies are needed to adapt DII calculations in different contexts and the varied number of components (defining a minimum) to be included in the calculation.

It is still fundamental to reinforce some characteristics of the diets of older adults [74,75], which results in less diversity and, therefore, can lead to problems regarding the calculation and discussion of DII. Besides, the DII calculation requires some special care when collecting food data. It is necessary to include, in the data collection, reminders to the interviewees in the form of a checklist. For example, spices such as garlic, ginger, onion, saffron, oregano, turmeric, pepper, and rosemary are items that are generally overlooked by the interviewer and the interviewee. From this perspective, it is crucial to notice that many of the studies included here are secondary to broader studies and, therefore, were not designed to investigate DII. Also, in Shivappa's publication, the authors highlight the need for studies comparing the sensitivity of using tools other than 24-h food recalls, for example, the food-frequency questionnaire (FFQ). As far as we know, this type of study has not been carried out until now. In our systematic review, Hayden et al. [46] adopted the FFQ as the tool for dietary collection, and Laclaustra et al. [52] adopted the food history. The choice of adequate methods and care to investigate and interpret food consumption seems to be fundamental to the reliability of DII.

4.3. Additional issues

The time elapsed from baseline to the outcomes assessment also deserves to be highlighted in the cohort studies. One cohort collected the dietary intake data at baseline and evaluated the outcome (cognition) after ten years of follow-up [46]. The other cohort [52] investigated the outcome (frailty) after three years follow-up. The food intake can suffer relevant changes throughout the time, which therefore demands intermediate evaluations. Hayden et al. [46] pointed out this aspect as a study limitation, but Laclaustra et al. [52] did not.

Another essential aspect that deserves attention is the choice of covariates. Although our systematic review confirmed the association between DII with cognition and frailty, it is fundamental to remember that successful aging depends on several factors, in addition to nutrition. Aging is a complex phenomenon and depends on genetics, lifestyle (including physical activity and other healthy habits), social activities, and disease control [52,76]. As such, many variables can contribute to the deterioration of cognition, frailty, and increase the risk of disabilities. Although all studies in this systematic review have some degree of confounding control, such as the inclusion of age and sex in statistical models, we noticed some critical lacks. For example, Frith et al. [47] considered cognition as the primary outcome and did not assess covariables such as level of education and income [77–79]. Likewise, some studies that assessed frailty [48–50] did not include physical activity and nutritional status as a covariate [80,81]. Kim & Park [50] used only age and energy intake as covariates and mentioned this reduced number of covariates as a limitation of the study. Laclaustra et al. [52] had no adjustment for race and education. None of the studies with frailty as an outcome evaluated depressive symptoms, a relevant factor in the development of frailty. Of the three studies that assessed cognition, one of them [51] also did not consider depression as a covariate. Finally, despite the rationale for the simultaneous investigation of frailty and cognition presented here, the interrelation between these outcomes was not considered in any of the studies.

In addition to the covariables, the food intake is also dependent on economic and social covariables. In our systematic review, the schooling showed to have an inverse association with an anti-inflammatory diet. Also, BMI and nutritional status from MNA showed to be associated with frailty.

4.4. Limitations and strengths of our study

Most studies included here were cross-sectional, and the cohort ones assessed the diet only at baseline. Therefore, our data do not allow conclusions of causality. Besides, we did not search unpublished studies; it is essential to remember that negative results (studies without the confirmation of their hypothesis) are generally not published, limiting drawing conclusions about evidence. On the other side, as far as we know, this is the first systematic review investigating the use of DII® and aging outcomes. DII is a relatively new index, and recently their authors discussed some lessons learned and their future direction [82]. We believe that our results can contribute to improving this index, pointing to the limitations of the published studies with older adults.

5. Conclusions and recommendations

The studies included in our systematic review showed that DII® is significantly associated with frailty, cognition, and risk of disabilities. However, there are some concerns, especially regarding the dietary data collection and DII calculation, lack of information about the numeric values of the DII scores, and some issues about the study's design; these issues impair a determination of evidence. Further studies, with sensitivity analysis of the different components of this index, are needed. Also, frailty and cognition are fundamental issues in older ages, both outcomes are multifactorial, and therefore particular care must be taken when choosing confounding variables. Despite these issues, DII showed to be a promisor tool in investigating the inflammatory potential of older adults.

Authorship

BMV and SMLR designed the study. The data was analyzed by BMV, MVLSQ and CMM. The manuscript was drafted by BMV and SMLR. The final version of the manuscript was approved by all authors prior to submission.

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Nothing to declare.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.10.003.

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Artigo 2 – Dietary patterns and sleep quality in young adults: a systematic review. Submetido à revista Sleep Health e negado. Atualmente está em ajuste para nova submissão.

Dietary patterns and sleep quality in young adults: a systematic review

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Abstract

Nutrition and sleep are essential factors for quality of life. Dietary pattern (DP) is defined by habitual food intake, broadly evaluating the individual's food intake-related factors. Both a priori and a posteriori criteria could verify DP's quality on health-related outcomes. Sleep is a cyclic physiological state critical for several health issues, which varies according to the life cycle and can be influenced by food intake. We aimed to evaluate associations between dietary patterns and sleep quality parameters of young adults. We conduct a systematic review (PROSPERO: CRD42020178801) following PRISMA guidelines. Inclusion criteria were observational studies conducted with young adult (18 to 44 years old), sleep time and quality parameters obtained from objective and subjective tools, a priori or a posteriori DP evaluation, and studies published in English, Spanish or Portuguese. In contrast, exclusion criteria were people with sleep disorders, shift workers, sleep is not a primary outcome, and studies describe women in early menopause. Of the 1952 articles found in SciELO, PubMed and LILACS, six comprised inclusion criteria. All included studies were cross-sectional and published between 2012 and 2020. The risk of bias was assessed by the NIH tool, ranged from 45.5% to 94.4%. Four articles showed significant associations between DP and sleep-related parameters. Vegetables and fruits were positively associated with sleep quality, whereas sweet intake was negatively associated. We note that potential confounders were treated in different ways in statistical analysis, difficulting comparison between studies. In three articles, the statistical models developed were not sensitive to the proposed analyzes. Therefore, the present review concludes that a better DP prioritizing fresh and minimally processed foods, especially fruits and vegetables, are associated with better sleep parameters. However, more studies are needed, with adequate sample size and a more careful analysis of confounding variables.

Keywords: Dietary pattern. Sleep quality. Young adults.

Introduction

Sleep plays a pivotal role in maintaining health, as several epidemiological studies have demonstrated.[1,2] Researchers have already shown that both short-sleep duration and poor sleep quality negatively affect several metabolic parameters.[3-6]

Lifestyle is among the variables associated with sleep quality, and diet assumes importance in this context. Several foods, nutrients, or food compounds can modulate sleep through different mechanisms.[7,8] For instance, w-3 fatty acids, especially docosahexaenoic acid (DHA), improve neuronal homeostasis and serotoninergic neurotransmission, while eicosapentaenoic acid (EPA) decreases brain inflammatory pathways.[9] High-glycemic index carbohydrates (HGC) increase insulin secretion, which indirectly affects the central tryptophan/large neutral amino acids uptake, increasing serotonin synthesis and consequent melatonin production.[10] L-ornithine seems to alleviate the stress by modulating the cortisol/DHEA-S ratio; this amino acid also stimulates GH secretion, increasing serotonin and, consequently, melatonin synthesis.[11] In contrast, caffeine is an adenosine receptor antagonist, and adenosinergic neurotransmission plays an essential role in non-REM sleep; therefore, caffeine can disrupt sleep architecture.[12,13]

Godos et al.[8] conducted a systematic review including school-age children, adolescents, and adults, and explored the relationship between the intake of different food groups and sleep quality. The authors found that healthy foods were associated with better sleep quality, while a higher intake of processed and sweetened foods showed contrary results. Dietary aspects can modulate several biomarkers of health and, consequently, sleep, for example, insulin sensitivity,[14] lipid profile,[15] adiposity,[16] and inflammatory status.[17-19]

On a broader view, studies of dietary patterns (DP) have identified that the high adherence to healthy patterns such as the Mediterranean DP can positively modulate sleep quality. On the other side, adherence to unhealthy patterns such as the so-called Western DP can lead to opposite results[20-22]. In this context, it is essential to reinforce the interrelated nature of dietary exposures. Although some compounds are proved to enhance many physiological functions, these potential benefits can be unfavorably reduced by other dietary components.[23]

The younger population, the target of our SR, is possibly one of the most affected by poor dietary quality due to high workload and social life; therefore, they are more prone to different health risks.[24-27] We hypothesize that these dietary habits can contribute to poor sleep quality. As such, we aimed to investigate the associations between dietary patterns and sleep parameters in younger adults.

Methods

We conducted a systematic review of the literature (SR), guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [28] and registered in PROSPERO (CRD42020178801; *due to the Covid-19 pandemic, it was registered automatically, exactly as submitted, which means that eligibility was not verified by PROSPERO*). The research question was: "Are dietary patterns associated with sleep quality in younger adults"? This question was developed and improved using the PI(E)COS strategy, detailed in **Table 1.**

The inclusion criteria were: Epidemiological studies (due to our aim to identify diet in the medium and long term), performed with younger adults (18 – 44 years old), evaluating sleep by objective (polysomnography or actigraphy) or subjective (validated questionnaires or isolated questions) methods; with diet investigated by diverse techniques (24h food recall, food diary or food frequency questionnaire; questionnaires identifying food groups and servings), and analyzing the DP by methods *a priori* or *a posteriori*. Also, we included only studies published in English, Portuguese, or Spanish languages. We excluded clinical trials, studies with sleep-related diseases such as sleep apnea, bruxism, jetlag, restless leg syndrome, and others; studies with women in the menopause transition; studies in which, instead of evaluating DP, investigated the intake specific nutrients; studies where the sleep was not the primary outcome; narrative or systematic reviews.

The databases consulted were PubMed/MEDLINE, LILACS and SciELO, with studies published up to April 4th, 2020. The following search strategy was used in all databases: ((((((((((((((((((((((((((((diet, Mediterranean) OR Mediterranean diet) OR diets, Mediterranean) OR dash diet) OR diet, dash) OR diets, dash) OR dietary approaches to stop hypertension diet) OR diet, vegetarian) OR diets, vegetarian) OR vegetarian, diets) OR lacto-vegetarian diet) OR diets, lacto-vegetarian) OR lacto-vegetarian diet) OR (diets, plant-based) OR plant-based diet) OR plant-based nutrition) OR nutrition, plant-based) OR lacto-egg vegetarian diet) OR diet, lacto-egg vegetarian) OR diets, western) OR western dietary pattern) OR dietary pattern) OR western dietary patterns) OR diets, occidental) OR occidental, diet) OR meat-sweet diet) OR diet, meat-sweet) OR diets, meat-sweet) OR meat-sweet diets))) AND ((sleep) OR sleep quality)").

To conduct our SR after the search in databases, we followed the steps described below:

Step 1: Careful reading of the titles and abstracts to exclude the ones not related to the research question, as well as the duplicates. This step was performed by the first and second

authors (JSV and MVLSQ) and checked by the fourth author (SMLR); a consensus meeting solved the divergences.

Step 2: Acquisition of the selected articles in total and perusal to identify in detail the inclusion and exclusion criteria. Two authors performed this step independently (JSV and MVLSQ), and the divergences were solved by a consensus meeting with the fourth author (SMLR). The data were extracted in an Excel spreadsheet containing authors, title, year and location of publication, information about being secondary or primary data, inclusion and exclusion criteria, hypothesis and objectives, total sample size, age, and sex; primary outcomes; definition of exposure and diagnostic criteria; characterization of exposition (variable of interest of our systematic review); confounders variables; statistical analyses; results; any other comments of interest.

Step 3: Assessment of the studies' quality, conducted independently by two authors (JSV and SMLR) and using the *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies* from the National Institutes of Health. A score was developed for better understanding this tool classification: "zero" was attributed to no attendance to an item; "0.5" to partial attendance; "one" to total attendance. A percentage was calculated to indicate the final quality score of each study, being the highest score attributed to the highest quality and lowest bias risk of the studies.

Step 4: In-deep analysis of the studies; performing a careful reading of the articles by three authors (JSV, CMM, and SMLR); further discussion of their strengths and limitations.

Results

Figure 1 shows the steps of the study. The literature search resulted in 1,952 publications, 1,760 from PubMed, 148 from LILACS, and 44 from SciELO databases. After excluding duplicates, 1,945 studies had the title and abstract screened and, 30 of them attended the eligibility criteria and were selected for a full reading. Further, six studies were included to continue the systematic review. The main reasons for exclusions were different age range, lack of evaluation, definition, or association with a DP, studies performed with jet lag syndrome or shift-workers, and literature review.

All the studies were published in English language; four were conducted in the United States of America,[29-32] one in Italy[33] and one in Iran.[34] Regarding the publication period, they were published between 2012 and 2020, being four of them published after 2017.[29-31,33] All the studies were cross-sectional; three of them were part of extensive cohort studies (NHANES;[32]

EAT Project;[30] TAAC[29]), and one was derived from a clinical trial.[31] All the studies evaluated the sleep parameters by questionnaires, which implies in subjective analyses. **Table 2** and **Table 3** summarize the studies' characteristics.

Summary of findings

Jansen et al.[31] in a secondary study derived from the "Encouraging Young Adults to Make Effective Nutrition Choices," included 1,444 participants of both sexes between 21 and 30 years old. Sleep quality was evaluated by selected questions of the Pittsburgh Sleep Quality Index (PSQI). The daily intake of fruits, juices, or vegetables (FV) was evaluated by *a priori* analysis, using validated questionnaires. In descriptive data, the participants showed an FV intake below the recommendations. Regarding sleep quality, 32% of the sample had a sleep duration below seven hours per night, and more than one-third reported insomnia symptoms.

In crude models' analysis, the higher consumption of FV presented significant associations with sleep quality, lower sleep latency, and fewer insomnia symptoms, but not with sleep duration; the associations with sleep quality and lower sleep latency remained significant in the adjusted models. These associations showed to be stronger in men.

In the inSOMNIA study, Gianfredi et al.[33], evaluated sleep disturbances and lifestyle habits (smoke, health status, and academic performance) in 117 undergraduate students between 20 and 43 years old, both sexes. Sleep disturbances were evaluated by the "Questionnaire on Sleep and Daytime Habits (S&DHQ)" and classified as: Difficulty in Initiating Sleep (DIS), Difficulty in Maintaining Sleep (DMS), Early morning awake (EMA), Non-Restorative Sleep (NRS), and Insomnia with Diurnal Symptoms (IDS). DP was evaluated a priori, using the adherence to the Mediterranean dietary pattern (MDP) by the PREDIMED questionnaire;[38] the authors also included questions related to other typical Mediterranean food, processed meat, and alcohol intake. As the main results, 94.9% of the participants had moderate adherence to the MDP, which can be considered a relatively healthy pattern. The prevalence of sleep disturbances was 18.8%, where 11.9% related IDS. Logistic regression models (adjusted for age, gender, BMI, and alcohol intake) showed no significant association between the MDP and the investigated sleep disorders. However, the secondary analysis showed a significant association between coffee, meat, and fish intake with EMA, DIS, and nocturnal insomnia. Also, eating whole grain bread was significantly and inversely associated with DMS; coffee consumption at least three times a day was significantly associated with DIS, DMS, and NRS. Eating sweets at least three times per week was significantly associated with NRS. The chi-square test showed a significant association between late afternoon coffee consumption and

DIS, DMS, Insomnia, and IDS. As a limitation of the study, the authors described the small sample size and the use of only subjective data.

Young et al.[29] performed a cross-sectional analysis from a cohort study including 462 young females (22.9 ± 0.45 years). They adopted the PSQI to evaluate sleep quality. The DP was investigated from a priori analysis, using questions extracted from two validated questionnaires; the questions investigated food groups' intake (fruits, vegetables, energy drinks, and sweetened drinks). Poor sleep quality was reported by 45% of the participants, and more than 50% of them had an intake of fruits and vegetables less than one portion per day. Also, around 21% consumed at least one sugary beverage per day, and almost 45% consumed some amount of high-calorie caffeinated drink per day. There was no significant association between fruit and vegetable intake and sleep quality in crude or adjusted models. In crude analysis, poor sleep quality was significantly associated with energy drinks, high-calorie coffee drinks, and fewer weekly days eating breakfast. These associations were no longer significant when adjusted for confounders (race, schooling, annual income, employment status, and BMI).

Xiao et al.[32] investigated the association between the a priori Healthy Eating Index (HEI) and sleeping time in a cross-sectional study extracted from the NHANES survey (combined results from four waves; 2005-2006; 2007-2008; 2009-2010; 2011-2012). The sample was composed of 896 non-pregnant women (20 to 44 years old) who completed two 24-hour dietary recalls (first by mobile examination center and second via phone 3-10 days later). Sleep duration was assessed by the question: “How much sleep do you usually get at night on weekdays or workdays?”. Authors categorized sleep duration as short (< 6 h), adequate (7-8 h), and long (> 9 h). Median sleep duration was 6.9 hours (SE=0.06); 34.3, 57.1, and 8.6% were classified as short, adequate, and long sleepers, respectively. The overall HEI score was 47.4 (SE=0.8); the short, adequate, and long sleepers had the HEI score of 45.5 (SE=1.4), 49.2 (SE=0.9), and 43.5 (SE=2.5), respectively. After adjusting covariables (age, ethnicity, and education level), women with long sleep duration presented lower diet quality, lower fruit intake, and high intake of empty calories than women with adequate sleep duration. In turn, short sleepers were not significantly associated with diet quality.

Haghighatdoost et al.[34] conducted a cross-sectional study with 410 younger female students (18 – 28 years old). A 168-item semiquantitative food frequency questionnaire assessed the diet. Then, four a priori methods were conducted, namely dietary diversity score (DDS), dietary energy density (DED), HEI, and mean/nutrient adequacy ratio (MAR). The sleep duration was extracted from 24h-physical activity recall and stratified in tertiles, the lowest tertile< 6h, the middle tertile from 6 to 8 h, and the highest tertile > 8h. About the sleep

duration, 35% of the participants presented <6h of sleep, and 45% had sleep duration between 6 and 8h per day. The mean fruit intake varied from 2.4 to 3.1 serving/day and vegetables from 2.9 to 3.1 serving/day across the sleep duration tertiles. The HEI index varied from 53.9 and 61.0 in the lower and highest tertile of sleep duration. The Dietary Energy density score was around 1.52-1.50 in all tertiles; the Dietary diversity score ranged from 5.3 in the <6h group to 6.2 in the >8h group. The Diversity score of fruits and Diversity score of vegetables varied from 1.0 to 1.5 on average across the tertiles of sleep duration. The HEI, DDS, and MAR scores were lower in the lowest sleep tertile than in the highest sleep tertile. The authors also investigate the associations considering food groups and nutrient sources. The intake of fruits, whole grains, and beans was smaller in the lower tertile of sleep duration than the highest tertile. Subjects in the lower tertile had higher energy and carbohydrate intake and lower protein and fiber intake when compared with the highest tertile.

The study of Ogilvie et al.[30] was part of the Eating and Activity in Teens and Young Adults study and evaluated sleep and dietary habits in 1,854 younger adults between 20 and 30 years old. Sleep variables (usual bedtime and waking time on both weekdays and weekends) were investigated using questions from previous studies; sleep quality was assessed from questions extracted from a depressive symptom questionnaire.[41] The authors calculated other indexes from these questions, namely, sleep variability, calculated from the difference between weekday and weekend time in bed, and sleeping time, measured by the averaging weekend and weekday bedtimes. The authors adopted a 151 items food frequency questionnaire (FFQ). They evaluated the intake of sugar-sweetened beverages, sugar-free beverages, and caffeinated beverages; the weekly habits of skipping breakfast and an annual intake of sports drinks were investigated using specific questions. Three different models of logistic regression were performed, based on adjustment variables (model 1 adjusted for age, gender, race, schooling, and marital status; model 2 adjusted for variables in model 1 added with depressive symptoms and physical activity level; model 3 adjusted for variables in model 2 added with time in bed and variability of sleep duration and quality). All the analyses, including the descriptive ones, were performed according to the sleep duration categories (<7 hours; 7-<8 hours; 8–9 hours; and ≥ 9 hours). Mean sleep duration of 8.3±1.2h per night was reported by the participants and, concerning sleep duration categories, 11.5% slept <7h/night, 26.6% slept between 7-8h/night, 36.2 slept between 8-9 hours per night, and 25.8% more than nine hours per night.

Regarding DP, participants consumed on average 0.9 servings/day of sugar-sweetened beverages, 0.7 serving/day of caffeinated beverages, and consumed breakfast and fast food on average 3.9 and 1.6 times per week, respectively. The dietary variables indicating poor DP

(energy drinks, sugar-sweetened beverages, fast food, and breakfast skipping) were significantly associated with late sleeping time. Less time in bed (which the authors used as a proxy of sleep duration) was associated with more caffeinated beverage consumption. More time in bed was associated with fewer sports drink consumption. From the sensitivity analysis, those who slept fewer than six hours per night skipped breakfast more frequently and consumed more sugar-sweetened beverages than those who slept 7–8 hours. Poor sleep quality, after adjustments, was significantly associated with energy drinks, sports drinks, and skipping breakfast. Sleep variability was associated with higher fast food and energy drink consumption.

Figure 2 shows the classification of the studies according to the NIH tool. The lowest score study was attributed to Haghighatdoost et al.[34] with 45.5%; Gianfredi et al.[33] achieved 50%., and the highest quality study was the one from Xiao et al.[32], with 94.4% of attendance of the criteria. The other three studies were classified from 70% to 77.7%. **Supplementary table 1.** contains details regarding the analysis of the risk of bias.

Table 4. describes the main confounders used by the studies. Race/ethnicity, BMI, and education were the covariables most used by the studies (four studies in total), followed by age, adopted by three studies. The remained covariables were used only in few studies (sex, relationship status, physical activity, anxiety/ depression in two studies: income, employment status, shift workers, stress/quality of life, alcohol intake, and time in bed by one study each).

Discussion

We aimed to confirm the hypotheses: -younger adults have a particular lifestyle that led to bad dietary habits; - these dietary habits are associated with poor sleep parameters. Six studies, ranging from medium and high quality, met our eligibility criteria. The studies included the age range from 20 to 44 years old, and three studies evaluated only females. The dietary patterns were investigated only *a priori,* with different instruments. Three studies used general indexes to define diet quality (adherence to Mediterranean diet, healthy eating index, and other indexes investigating the diversity, energy density, and energy adequation). Three studies used specific questions identifying markers of healthy (fruits and vegetable intake, but also whole grains) or unhealthy (sugary and salty snacks, caffeinated and sugary beverages) dietary patterns. The participants' dietary quality, in general, showed to be from moderate to low. The studies evaluated sleep quality by self-perception[30,32,34] or validated questionnaires,[29,31,33] and none used objective methods. Putting the results together, we can describe de sleep quality of

the samples as varying from moderate to low. Therefore, both dietary and sleep information turn it challenging to compare the results of our SR.

The healthier dietary patterns (mainly composed of fruits, vegetables, whole grains) showed significant association with favorable sleep parameters (sleep duration, quality, and lower sleep latency). Fruits and vegetable intake could promote better sleep quality due to micronutrients and antioxidants compounds, which can optimize the synthesis of hormones (such as melatonin) and neurotransmitters.[42] Contrariwise, unhealthy dietary patterns, represented by a high intake of sweets, sweetened drinks, snacks, and fewer days per week eating breakfast, showed opposite associations with sleep quality, such as different insomnia symptoms (difficulty initiating early morning awake and non-restorative sleep). Some of the studies also showed that energy drinks, high-calorie coffee drinks, or caffeinated drinks could compromise sleep quality [33]. Although caffeine's effect on sleep is not consensual,[43] many studies pointed its intake to be related to sleep issues; caffeine is considered an adenosine receptor antagonist, and adenosinergic neurotransmission plays a role in non-REM sleep.[44] Carbohydrate intake has also been related to sleep, and the restriction of this nutrient might change sleep architecture, increasing slow-wave sleep and reducing REM sleep.[45]

Afaghi et al.[10] showed that high-glycemic-index meals reduced sleep onset latency. However, the effects of carbohydrate intake on sleep are mixed. For instance, recently, Vlahoyiannis et al. [45] in a meta-analysis and meta-regression, verified that compared to high carbohydrate, low carbohydrate intake moderately increased duration and proportion of N3 sleep stage, while high carbohydrate intake prolonged REM-sleep stage duration. Also, according to these authors, carbohydrate quality did not affect sleep stages.

Our results pointed that both shorter and longer sleep durations are associated with unhealthy DP. For example, Xiao et al.[32] found that longer sleep duration was associated with lower consumption of fruits and higher intake of empty calories. In turn, Haghighatdoost et al.[34] identified that fruit, whole grains, and beans intake was lower in the lower sleep time tertile. Moreover, the dietary indexes adopted by the authors showed worse scores in the shorter sleep duration group. The relationship between sleep duration and diet quality has been described as a U-shape relationship; most prolonged sleep lead to low diet quality.[35] Sleep duration has not a linear association with health outcomes, being the short and long sleep duration associated with increased risk for metabolic diseases as diabetes risk and cardiovascular events [46], depression [47], and all-cause mortality.[48]

We selected, to this SR, studies that defined specific dietary patterns; our intention in this aspect was to avoid the discussion of single nutrients since there are numerous interactions

between food components. In the same perspective, we included only epidemiological studies and excluded clinical trials, trying to investigate the daily habits of the persons and not any temporary interventions. Our data showed that the best sleep quality was associated with DP based on high consumption of vegetables, whole grains, legumes, olive oil, and fish; and based on low intake of red meat, refined sugar, processed foods, and stimulants beverages. Our findings were following Godo's et al.[8]; these authors performed another SR with younger and older adults, and verified that healthy eating patterns were associated with favorable sleep parameters. Surprisingly, Gianfredi et al. [33] did not find a significant association between the Mediterranean dietary pattern, one of the most studied DP due to its healthy features, and sleep-related parameters after the inclusion of the adjusting variables. These findings can prove the importance of the covariables in the analyses. Sleep is affected by factors such as sex, age, body composition, environment, acute pre-sleep behaviors, light, among others;[49-54] lifestyle aspects beyond diet include physical activity level[55] and alcohol intake.[56] Only one study of our SR controlled their results by physical activity,[31] only one considered alcohol intake,[33] and one study[29] controlled analysis by age. Also, sleep quality is highly influenced by socioeconomic status,[57] especially in younger individuals.[58] Low socioeconomic status and family problems may be stress factors that affect sleep quality,[56] although this may be controversial and influenced by sex.[59,60]

For these reasons, to understand how the DP affects sleep parameters, it is essential to control adjustment variables or covariables. The studies included in our SR were heterogeneous in this regard. The study of Jansen et al.[31] was the one that included the highest number of covariables (nine in total), followed by Olgivie et al.[30] (seven covariables), and Young et al.[29] (six covariables). The different choices by the studies turn it difficult the comparison between the selected publications.

As confirmed by the included studies in this SR, the poor diet quality, characterized by low intake of fruits and vegetables and frequent intake of sweetened and stimulants beverages, is probably related to an increased inflammatory process. Considering that the increase in the inflammatory process is also associated with poor sleep quality[61] we can suggest that this increased inflammatory process might link poor diet quality and sleep.

Several mechanisms can explain the relationship between sleep and the inflammatory process. For example, pharmacological administration of IL-6 and IFNγ suppress early-night slow-wave sleep (SWS) and NREM and decreases REM sleep in humans [62]. Chronic HPA-axis activation leads to a pro-inflammatory state that could decrease sleep duration, induce sleep fragmentation, and increase REM sleep, with reciprocal loss of SWS.[63,64] Still, the lowest

inflammatory state increase total sleep duration, sleep continuity, and NREM sleep [65]. The gut-brain axis can explain sleep quality and inflammation. High-fat diets (typical in the occidental dietary pattern) may affect gut microbiota composition and activity, leading to changes in circadian rhythm-related mediators [66,67]; possibly, the vagal nerve is involved in these processes. However, further studies are required to elucidate this mechanism. Likewise, obesity can increase the inflammatory status since the fat content in adipocytes attract M1 macrophages and other immune cells, signaling an inflammatory status. Consequently, the adipocytes reduce adiponectin secretion and secrete inflammatory cytokines. In our SR, four out of our six studies considered the BMI as covariable.[29,31,33] Short sleep duration has been associated with higher BMI,[60,68,69] and weight gain worsens sleep quality.[70]

Some limitations of this systematic review deserve to be mentioned. First, all the studies were cross-sectional, which does not allow inferring causality. Sleep can be related to diet in a bidirectional feature. Sleep debt also unbalances homeostatic pathways (i.e., ghrelin and leptin)[71] and activates the hedonic system, responsible for food reward mechanisms.[72] Both paths could increase food intake, especially more palatable food (rich in sugar and fat). In turn, better sleep quality is related to a better daytime quality of life, resulting in better food choices with lower preferences for unhealthy foods.[73] Finally, sleep debt triggers a stress system that increases anxiety and negative emotions, increasing anti-anxiety foods intake.[74]

The second limitation is that all the included studies adopted subjective investigation of sleep. Sleep perception is quite complex and can be influenced by several factors, impairing the study results' interpretation.[75] Previous studies investigating the accuracy of the self-reported and validated sleep questionnaires compared to objective methods found moderate agreement [76-78]. However, studies that evaluated only sleep time, instead of subjective questionnaires, presented a higher risk of bias because sleep time and bedtime are different, leading the information to be over-or under-estimated.[78]

The third limitation is the significant differences between studies regarding the definition of DP. Our results pointed that using indexes like MDP or HEI (therefore more embracing methods) can show different results compared to food groups' use, as shown in Gianfredi' s et al.[33] study.

Concluding, we found that dietary patterns rich in vegetables, fruits, and whole grains seem to be associated with the most favorable sleep parameters. On the other hand, consuming sugar, caffeinated drink, and empty calories was associated with the worst sleep quality. However, the more embracing definitions of DPs, or the inclusion of different covariables, showed less conclusive results. Further studies, with longitudinal design and more

homogeneous concerning covariables, would allow more conclusive systematic reviews and even metanalyses.

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Table 1. PI(E)COS strategy used to reinforce the research question

Population (P)	young adults (18 to 44 years old);
Intervention/exposure (I/E)	dietary pattern;
Comparison (C)	any kind of comparison or without comparison;
Outcome (O)	sleep quality;
Study type (S)	epidemiological studies (cross-sectional, cohort and case control).

Table 2. General characteristics of the studies included in the systematic review

Author and year	Country	Study design	Original study (When Applied)	Sample size, age and sex	Objective(s)	Dietary assessment tool to identify dietary patterns	Method of sleep assessment
Jansen et al.[35]	USA	Cross sectional	"Encouraging Young Adults to Make Effective Nutrition Choices" Randomized clinical study	1444 21-30 years old M/F	To evaluate the association between the duration and quality of sleep with the consumption of fruits and vegetables	Two-item instrument to ascertain the number of serving of fruits and vegetables [36]	Pittsburgh Sleep Quality Index (PSQI) [37]
Gianfredi et al.[33]	Italy	Cross sectional	-	117 20-43 years old M/F	To determine the prevalence of sleep disorders among nursing students	14-item Questionnaire of Mediterranean diet adherence [38]	Sleep Questionnaire and Daytime Habits [39]
Young et al.[29]	USA	Cross sectional	"Trial activity for adolescents girls-TAAC"Cohort study	462 mean 22,9+/-0,45 years old F	To evaluate the association of dietary behaviors with sleep quality among young adult women	Questions derived from the Youth Risk Behavior Survey 2009 for food and screening tool for beverages [40]	Pittsburgh Sleep Quality Index (Complete)
Xiao et al.[32]	USA	Cross sectional	NHANES study	896 20-44 years old F	To examine the association between sleep duration and quality of diet among US women within 5 years of childbirth.	Two 24-h dietary recalls and Healthy Eating Index-2010 calculation	One question extracted from NHANES questionnaire: "How much do you usually sleep at night on weekdays or work?"

Haghighatdoost et al.[34]	Iran	Cross sectional	-	410 18-28 years old F	To determine the association between general/abdominal obesity, diet quality indices and different good groups consumption with sleep duration	168-item semiquantitative food frequency questionnaire plus HEI, DDS, DED and MAR indexes	Sleep time reported from a physical activity diary
Ogilvie et al.[30]	USA	Cross sectional	"Eating and Activity in Teens and Young Adults - EAT Project" Cohort study	1854 20-30 years old M/F (55.6 female)	To test the hypothesis that inadequate sleep is associated with the consumption of a greater amount of caffeinated and sweetened drinks, and report skipping breakfast and eating in fast food restaurants	Questions about sport and energy drinks during the last year, and questions about skipping breakfast and eating in fast foods during the last week (questions derived from the EAT-III Project). Also, a previously validated 151-item FFQ investigated sugar-sweetened, sugar-free, and caffeinated beverages	Questions taken from the two scales, the Night *Eating Diagnostic Scale* and *Kandel and Davies depression questionnaire*, both validated and used in previous publications.
Legend: Healthy Eating Index (HEI), Dietary energy density (DED), Mean adequacy ratio (MAR), Dietary diversity score (DDS); FFQ= food frequency questionnaire							

Table 3. Statistical methods and results of interest of the studies with statistical significance										
Author and year	**Statistical method**	**Main results**								
		Categories of sleep time (or time in bed)				**Sleep quality**	**Latency time**	**Insomnia symptoms**	**Sleep variability**	**Sleep duration**
Jansen et al.[35]	Kruskal Wallis Chi square Linear regression with some sensitivity analysis	<7h NS	7-8h NS	8-9h NS	>9h NS	Higher sleep quality group reported eating 37% more portions of FV per day than the lowest sleep quality group (95% CI 0.07, 0.68; p<0.0001).	The longest sleep latency (>45 min to fall asleep) had less 25% consumption in FV servings per day compared to the fasted latency ones (95% CI -0.44 -	The association between low FV intake and the presence of three or more insomnia symptoms (p=0.02) was not sustained after covariates adjustments (p.0.05)	NR	NS

							0.05; p<0.0001)			
Gianfredi et al.[33]	Chi square T test Multivariate logistic regression adjusted for age, gender, BMI and alcohol intake	NR	NR	NR	NR	NRS *vs* intake of coffee (>3x/day; aOR: 3.4; 1.4-8.3 95% IC; p=0.009); and sweets (> 3x/week; aOR: 3.6; 1.4-9.2; p 0.00)	DIS *vs* fish intake (> 3x/ week; aOR: 14.1; 1.0-194.7 95%IC; p=0.04); and coffee intake (>3x/day; aOR: 19.2; 4.2-87.2;p<0.001)	DMS *vs* whole bread intake (>3x/week; aOR:0.1; 0.0-0.9 95%IC; p= 0.04) and coffee intake (>3x/day; aOR: 11.2; 2.6-49.1;p=0.01); NI *vs* with fish intake (> 3x/ week; aOR: 16.6; 13-218.3 95%IC; p=0.003) and coffee	NR	NR

								intake (>3x/day; aOR: 19.6; 5.7-67.5;p<0.001); IDS *vc* coffee intake (>3x/day; aOR: 30.1; 5.4-167.5;p<0.001).		
Young et al.[29]	Chi Square Fischer test Wilcoxon rank test Linear regression analyses	NR	NR	NR	NR	Poor sleep quality was associated with reporting consuming energy drinks (p = 0.008), high-calorie coffee drinks (p = 0.0002) and fewer days per week of eating breakfast (p . 0.002). NS after	In adjusted models, drink at least one high-calorie coffee drink per day was associated with longer sleep latency (+8.7 min)	NR	NR	NS

						adjustment in any parameter	compared with reporting no high-calorie coffee drink consumption (p.0.04)			
Xiao et al.[32]	ANOVA Chi Square Linear regression: some covariates were tested in sensitivity models.	≤ 6 (n = 352) HEI score = 45.4 ± 1.4	7-8h (n = 483) HEI score = 49.2 ± 0.9	-	≥ 9h (n = 61) HEI score = 43.5 ± 2.5	-	-	NR	NR	NR
Haghighatdoost et al.[34]	Multivariate analysis of variance Chi Square	< 6h (n = 144) HEI score = 53.9 ± 15.1 p = 0.002 (versus > 8h)	6-8h (n = 187) HEI score = 58.7 ± 15.8	>8h (n = 79) HEI score = 61.7 ± 17.0 High DDS (p = 0.001) and MAR (p = 0.04)	-	-	-	NR	NR	NR

				score versus < 6h tertile High fruit (p = 0.04), whole grains (p = 0.04) and beans (p = 0.04) intake versus < 6h tertile						
Ogilvie et al.[30]	Adjusted probabilities standardized to the total population were calculated for each sleep category in the logistic regression models, and these probabilities were used to calculate prevalence ratios for each outcome. Model 1 adjusted for age, sex,	<7h (n=203) Time in bed <7h was associated with higher intake of caffeinated drinks, which was different from the	7-8h (n=471) NS	8-9h (n=642) NS	≥9h (n=457) NS	-	-	The answer "very much" was associated with caffeinated beverages [Model 1=mean intake 0.83 (95% CI 0.71, 0.95)] and SSB [Model 1=1.06	Sleep variability >1,5h was associated with sugar free drinks [(Model1=(mean intake=0.39; (95%CI =0.32, 0.47), and with fast-food consumptio	Sleep time after 12:30AM was significantly associated with caffeine intake [model 1: 0.80 (0.71, 0.90))],with SSB[Model 1=

	race/ethnicity, education, marital status; Model 2 added depressive symptoms and physical activity. For models with sleep variability, timing, and quality as the exposure, model 3 added time in bed.; two covariates were tested in sensitivity models (time in bed lesser than 6h and BMI).	other time intervals, in Model 1[0.87 (0.71, 1.04)]						(0.89, 1.22)]; Sugar free beverages [Model 1= 0.42 (0.33, 0.52)] and breakfast consumption [Model 1=3.27 (3.02, 3.51); Model 2=3.42 (3.16, 3.68); Model 3=3.43 (3.17, 3.69)]	n in the three models (Model 1=1.77 (1.60, 1.93); Model 2= 1.76 (1.59, 1.93) Model 3=1.77 (1.60, 1.94))	1.05 (0.93, 1.18); Model 2= 1.04 (0.92, 1.16); Model 3= 1.04 (0.91, 1.16)], breakfast consumption [Model 1= 3.18 (2.97, 3.39); Model 2= 3.21 (3.00, 3.42); Model 3=3.19 (2.97, 3.40)] , fast food consumption [model 1=1.70 (1.54, 1.86) and model 3=1.70 (1.54, 1.86)]

[1]evaluate bed time
NS = not significant; NR = not rated; serving/d = serving per day; DIS: Difficulty in initiating sleep; DMS: Difficulty in maintaining sleep; NRS: Non-restorative sleep; NI: Nocturnal insomnia; IDS: Insomnia with diurnal symptoms.

Supplementary table 1. Quality assessment of the articles included using the NIH tool

NIH Questions	Janse n et al.[35]	Gianfredi et al.[33]	Young et al.[29]	Xiao et al.[32]	Haghighat doost et al.[34]	Ogilvi e et al.[30]
1. Was the research question or objective in this paper clearly stated?	1	0	1	1	1	1
2. Was the study population clearly specified and defined?	1	1	1	1	0,5	1
3. Was the participation rate of eligible persons at least 50%?	NA	1	NA	1	NR	NA
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	1	0,5	1	1	0	0,5
5. Was a sample size justification, power description, or variance and effect estimates provided?	0	0	0	1	0	0
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	NA	NA	NA	NA	NA	NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NA	NA	NA	NA	NA	NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	1	0,5	1	1	1	1
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1	1	1	1	1	1
10. Was the exposure(s) assessed more than once over time?	NA	NA	NA	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	1	0,5	1	0,5	1	1
12. Were the outcome assessors blinded to the exposure status of participants?	CD	NA	CD	NA	CD	CD
13. Was loss to follow-up after baseline 20% or less?	NA	CD	CD	NA	NA	NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	1	0,5	1	1	0	1

Total	7 points (77,7%)	5 points (50%)	7 points (70%)	8,5 points (94,4%)	4,5 points (45%)	6,5 points (72,2%)

1 = yes; 2 = no; NA = not applicable; CD = cannot determine; NR = not reported; percentage calculated from the exclusion of non-applicable items

Figure 1. Flowchart of representation of the study selection process

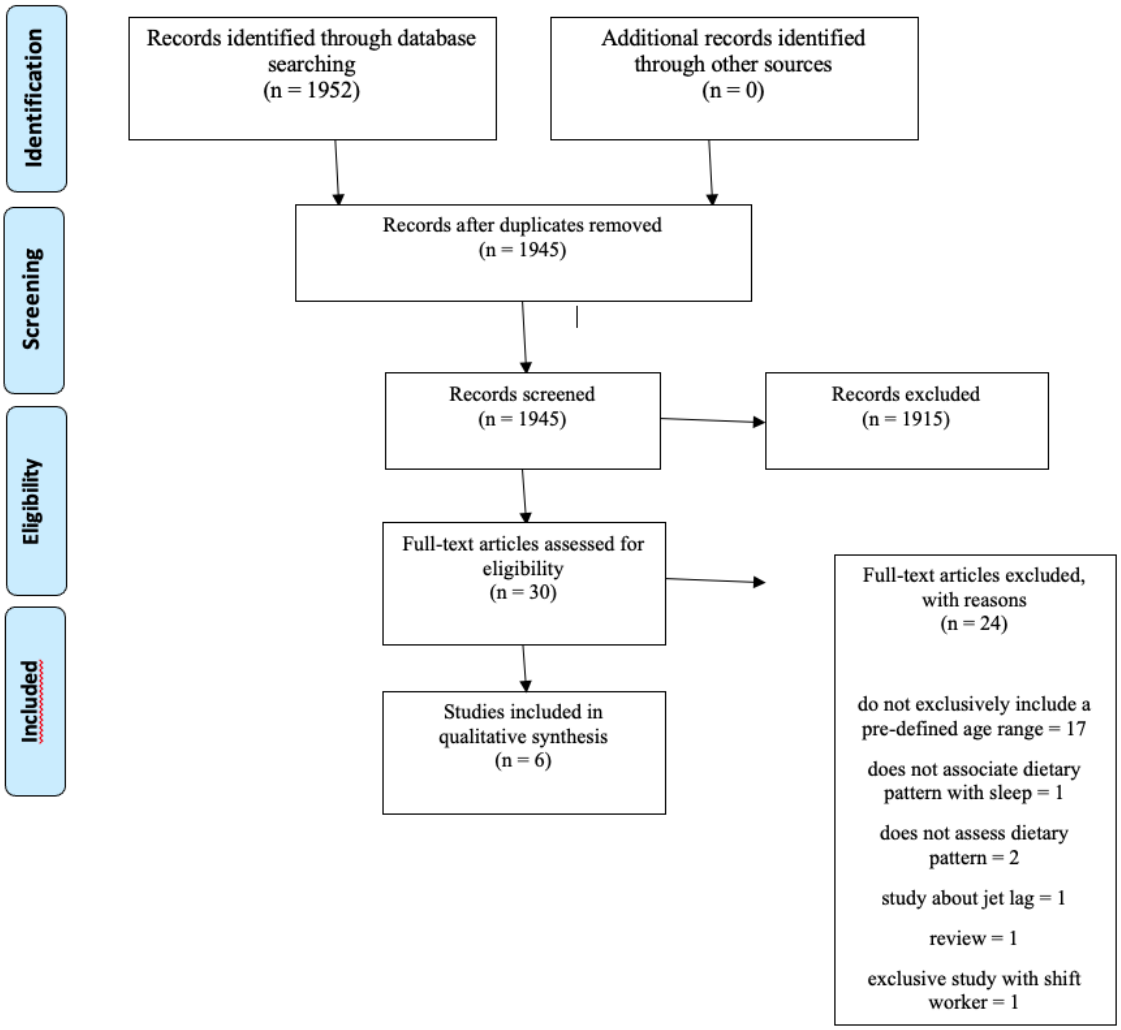
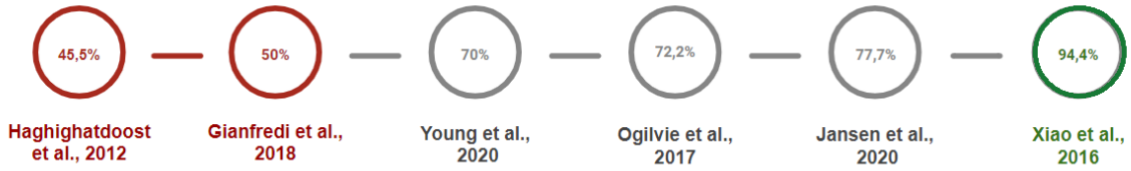


Figure 2. Percentage of achievement the quality criteria proposed by the NIH tool.

Higher risk of bias Smaller risk of bias



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ORIGINAL PAPER

Covid-19 Social Distancing, Lifestyle and Health Outcomes Among Persons Living with HIV (PLWH): A Web-based Survey

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Abstract
We investigated changes in lifestyle, depressive symptoms, self-perception of health, and body weight changes of persons living with HIV (PLWH) during the COVID-19 social distancing (SD). In a Web-based cross-sectional survey, participants (n = 406) were questioned about lifestyle and health status before and during SD. Most responders were men, 50 + years old, high education level; 49.8% had their income reduced during SD. About 9% were diagnosed with COVID-19, of whom 13.5% required hospitalization. During SD: - most participants did not change their food intake, although 25% replaced healthy foods with unhealthy ones; -more than half mentioned poor sleep quality; -about 50% increased their sedentary behavior. Depressive symptoms (reported by 70.9%) were associated with sedentary behavior, poor sleep quality, and reduced income. About one-third had a negative perception of their health status, which was inversely associated with practicing physical exercises and positively associated with sedentarism and poor sleep quality. More than half increased their body weight, which was associated with a lower intake of vegetables. The older age reduced the odds of the three outcomes. Carefully monitoring PLWH regarding SD will enable early interventions toward health.

Keywords COVID-19 · HIV · Lifestyle · Depressive symptoms · Body weight · Health

Resumen
En este trabajo investigamos los cambios en el estilo de vida, síntomas depresivos, autopercepción de salud y cambios en el peso corporal de las personas que viven con el VIH (PVCV) durante el distanciamiento social (DS) de COVID-19. En una encuesta transversal en línea, se preguntó a los participantes (n = 406) sobre el estilo de vida y el estado de salud antes y durante el DS. La mayoría de los encuestados eran hombres, mayores de 50 años, con alto nivel educativo. El 49,8% tuvo una disminución en sus ingresos durante el DS. El 9,1% fue diagnosticados con COVID-19, de los cuales 13,5% requirió hospitalización. Durante el DS: - la mayoría de los participantes no cambió su ingesta de alimentos, aunque el 25% reemplazó los alimentos saludables por los no saludables; más de la mitad mencionó mala calidad del sueño; cerca del 50% aumentó su comportamiento sedentario. Los síntomas depresivos (referidos por el 70,9%), fueron incrementados por el sedentarismo, la mala calidad del sueño y reducción de la renta. Cerca de un tercio tenía una percepción negativa de su estado de salud, que se redujo con la práctica de ejercicio físico y aumentó con el sedentarismo y la mala calidad del sueño. Más de la mitad aumentó su peso corporal, lo que se asoció con una menor ingesta de vegetales. Una edad más avanzada redujo las probabilidades de los tres desenlaces. El monitoreo cuidadoso de las PVCV con respecto al DS permitirá intervenciones tempranas para la salud.

Palabras clave: COVID-19 · VIH · estilo de vida · síntomas depresivos · peso corporal · salud

Introduction

The COVID-19 pandemic reached impressive numbers of

Extended author information available on the last page of the article

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persons infected and deaths globally [1] (https://coronavirus.jhu.edu/map.html). Given the absence of effective treatment, the slow pace of vaccination, particularly in low- and middle-income countries, and the emergence of new variants, social distancing (SD) has been necessary to reduce the spread of SARS-CoV-2.

Despite having well-recognized favorable effects in reducing viral transmissibility, SD can promote worrisome behavioral and psychological consequences. Recent data have shown an increased incidence of mental disorders during the pandemic, especially in physically or socially vulnerable groups [2–6].

A longer time spent at home enhances the possibility of unfavorable lifestyle changes [7–11]. For instance, Ammar et al. [12] performed an international online survey showing that different levels of SD resulted in reduced physical activity, increased sitting time, and increased unhealthy eating habits. In another context, a study conducted during Israel's first quarantine [13] compared persons under treatment in a specialized obesity clinic with individuals under no medical follow-up. In that study, patients under medical follow-up presented better eating and physical activity behavior and showed a lower prevalence of mood disorders; we assume that this indicates the importance of engagement in health-promoting strategies with professional follow-up during the pandemic.

The impact of SD in different populations may vary considerably, depending on local, social, economic, cultural, and political contexts. Here, we intend to consider the vulnerability of persons living with HIV (PLWH). We hypothesize that this population group is at increased risk of experiencing unfavorable effects of SD for many reasons. They often face HIV stigma and discrimination, are more likely to live alone and be socially dissatisfied [14, 15], and have to cope with residual effects of HIV infection and side effects of antiretroviral therapy (ART) [16]. COVID-19-associated uncertainty and insecurity may impact PLWH in particular [15].

During the COVID-19 SD, adoption of an inappropriate lifestyle may compromise health, raising concerns about the risk of developing or worsening metabolic disorders and chronic diseases [17, 18]. We aimed to explore lifestyle changes and associated outcomes among PLWH during COVID-19 SD. There have been no previous reports in this regard, as far as we know.

Methods

We conducted a web-based cross-sectional survey from November 2020 to January 2021. The convenience sample was composed of patients registered at the HIV outpatient reference clinic affiliated with the University of São Paulo, Brazil, where 3,145 adults living with HIV are under multidisciplinary clinical follow-up. After having basic information retrieved from their medical records, patients with an active phone number were sent an app-based message briefly describing the study's aims and confidentiality and inviting them to participate. Those who accepted were invited to read details about the study and sign a consent form. After giving their informed consent, participants were asked to fill up an e-questionnaire settled at a web application called Google Forms®. The study was approved by the Institutional Review Board (protocol # 4,285,897).

The questionnaire, which was previously pilot-tested, included multiple-choice questions and intended to disclose changes in lifestyle by comparing information concerning attitudes and behaviors exhibited before and during COVID-19-SD.

The questions covered the following aspects. Age was reported in years and the gender in categories (male, female or other); formal education was informed according to the highest level of formal schooling. Participants were questioned about their employment status before and during SD and whether they had any change in income. They were questioned if they had been diagnosed with COVID-19 and whether they needed hospitalization. They also provided information about the degree of experienced SD. The presence of depressive symptoms was investigated using the CES-D-4 [19], which includes four questions related to satisfaction with and meaning of life, life insecurity, and happiness. An unfavorable answer to any of these questions characterizes the presence of depressive symptoms. Participants informed their self-perceived health status [20] and reported any changes in body weight during SD. Diet-related questions [20] investigated the number of weekly days they consumed different foods before and during SD. We organized the questions into three sets. The first set considered healthy eating markers, protective against chronic diseases (beans, raw and cooked vegetables, whole fruits, and fish). The second set included unhealthy eating markers (sodas and soft drinks, sweets and candies, and snacks replacing meals), and the third comprised the foods considered by different studies as neutral or controversial regarding chronic diseases risk (fruit juices, milk, red meat, chicken, or other poultry) [21, 22]. Questions about physical activity [23] included details about the type and location of the activity and the number of weekly days and daily duration of each activity. From the answers, we created a variable regarding practicing or not physical activity. Participants were asked about changes in their sitting time in front of the TV or the computer, cell phone, or other devices during SD. The diet, the self-perceived status, and physical activity questions were adapted from Brazilian epidemiological studies

[20–23]. Sleep parameters were investigated with questions adapted from the Pittsburg Sleep Quality Questionnaire [24], including self-evaluation of sleep.

Data analyses

Continuous variables were presented as mean and standard deviation or median and range (depending on data distribution), and categorical data were presented as frequencies. We performed various logistic regression models to investigate the associations between the health outcomes and lifestyle information, as described below.

Dependent variables: (i) presence of depressive symptoms ("yes" against the reference "no"); (ii) self-perceived health status "regular, bad, or very bad" against the category" "good or very good" as reference) and (iii) changes in body weight (reference category "did not change or reduced" against the category "increased").

Independent variables (during SD): food intake (reference intake category "moderate" against "low" and "high"), physical activity (categories "did not practice" as a reference against "practiced"), sedentary behavior ("increased" and "reduced" against the reference "maintained" the sitting time), and sleep quality (reference category "good" against "bad"). We maintained one dependent variable at a time, as follows: (i) Crude models for each health and each lifestyle variable; (ii) Multiple models including the dependent variables and all the dietary questions (healthy, unhealthy, and neutral/controversial eating markers); (iii) Multiple models including the dependent variables and physical exercises practice and sedentary behavior; (iv) Multiple models including the dependent variables, and simultaneous inclusion of dietary intake, sleep quality, physical activity practice, and sedentary behavior questions; (v) We added to the previous model the sociodemographic variables (sex, age, and changes in income). Analyses were performed using the Stata version 14 (Stata Corp College Station, USA), adopting a statistical significance of 5%.

Keeping in mind that the pandemic could more negatively impact women and persons who are less educated (essential workers), we performed the descriptive and logistic regression models considering two subgroups: (i) only women and (ii) only people at lower levels of education.

Table 1 Sociodemographic features of the sample, clinical and behavioral information about COVID-19 (n = 406)

Variables	n	%
Sex		
Women	127	31.3
Men	279	68.7
Age interval (years old)		
≤ 30	21	5.2
31–40	49	12.1
41–50	96	23.6
51–60	182	44.8
60 +	58	14.3
Education		
Up to middle school	39	9.6
Incomplete high school	129	31.6
Complete or above high school	237	58.4
Missing answer	1	0.2
Employed during SD		
No	138	34.0
Yes	268	66.0
Family income during SD		
Same as before	184	45.3
Increased	20	4.9
Decreased	202	49.8
COVID-19 diagnoses	n	%
No	369	90.9
Yes	37	9.1
In case of infection, hospitalization due to COVID-19		
No	32	86.5
Yes	5	13.5
Behaviour during social distancing		
Stayed in complete SD	59	14.5
Leave home only for mandatory or essential activities	308	75.9
Avoided agglomeration but leave home for non-essential activities	39	9.6
Remote working due to SD (from the ones who were working)		
No	154	55.2
Yes	125	44.8
Number of medical consultations in 2020		
None	40	9.9
One	168	41.5
Two	133	32.8
Three or more	64	15.8

Results

Out of 3,145 patients registered at the clinic, 1,968 were sent an app message, and 414 responded to the questionnaire. We excluded eight responders who were not HIV-infected, leading to a final sample of 406 PLWH. Material S1 Figure describes the steps to achieve the final sample.

Demographic, socioeconomic characteristics, and information regarding COVID-19 infection are shown in Table 1. Most responders were men and older than 50 years. More than half reported having a higher education degree and were employed. Nevertheless, 49.8% reported having reduced their income during SD. Among participants, 9.1% reported having acquired COVID-19, of whom 13.5% needed hospitalization. Most participants complied with COVID-19 SD

recommendations of staying at home or leaving home only for essential activities; half of them have worked remotely. The number of visits to the outpatient reference clinic during 2020 was one or two for most of the sample, the usual number of visits before the COVID-19 pandemic.

Table 2 depicts mental and physical health status and sleep aspects before and during SD. The percentage of self-evaluation of health as "regular, bad, or very bad" increased during the SD, from 12.1 to 30%. More than half of the participants referred to increasing their body weight during the SD (56.9%). Almost 80% showed depressive symptoms during SD, more than twice the observed before SD (28.8%). All the CES-D questions worsened during SD (S1 Table). Also, 39.6% of the sample described poor sleep quality before SD, a proportion that increased to 54.6% during SD. The number of sleep hours did not show any observable difference among patients who slept poorly. INSERT FIGURE S1 after this paragraph

Table 2 Presence of depressive symptoms, body weight changes and self-perception of health, sleep quality before and during the social distancing (SD), with two categories (n = 406)

Variables	Before SD	During SD
	n (%)	n (%)
CES-D classification		
Presence of depressive symptoms	117 (28.8)	288 (70.9)
Absence of depressive symptoms	289 (71.2)	118 (29.1)
Perceived health status		
Good or very good	357 (87.9)	284 (69.9)
Regular, bad or very bad	49 (12.1)	122 (30.1)
Self-referred body weight changes		
Not changed or reduced		175 (43.1)
Increased		231 (56.9)
Sleep quality and time of sleep		
Good (6–8 h)	78(19.2)	42 (10.4)
Good (< 6 h)	155 (38.2)	104 (25.7)
Good (> 8 h)	12 (3.0)	38 (9.4)
Total of participants with good sleep quality	*245 (60.4)*	*184 (45.5)*
Poor (6–8 h)	83 (20.4)	108 (26.7)
Poor (< 6 h)	65 (16.0)	74 (18.3)
Poor (> 8 h)	13 (3.2)	39 (9.6)
Total of participants with poor sleep quality	*161 (39.6)*	*221 (54.6)*

Table 3 Physical exercise practice and sedentary behavior during social distancing (SD) (n = 404)

Physical activity and sedentary behavior	n (%)
Physical exercise information	
Performed any type of physical activity during the SD	173 (42.8)
Did not perform any type of physical activity during the SD	231 (57.2)
Sedentary behavior- sitting time	
Daily time watching TV	
Not changed	177 (43.6)
Reduced	28 (6.9)
Increased	201 (49.5)
Daily time on the computer, mobile phone or video games	
Not changed	177 (43.7)
Reduced	29 (7.2)
Increased	199 (49.1)

Figure 1 shows changes in the intake of the individual foods during SD. Although most participants did not change their overall intake, healthy eating markers, particularly vegetables and beans, reduced their ingestion by 23% and 16%, respectively. In turn, the intake of the unhealthy eating markers increased in an expressive proportion of participants (snacks replacing meals by 24.7%, sweets and candies by 31.4%, and soft drinks by 16.8%). A reduction in red meat intake was also observed in 22.7% of the sample. S2 Table describes the levels of eating markers before and during the SD.

According to Tables 3 , the proportion of 42.8% of the total sample reported performing any physical exercise during SD. Exercises performed at home were informed by 32.7%, while 22.7% practiced exercises outside the home (S3 Table); exercise types were distributed between aerobic (16.9%) and anaerobic types (15.1%), and mixed exercises

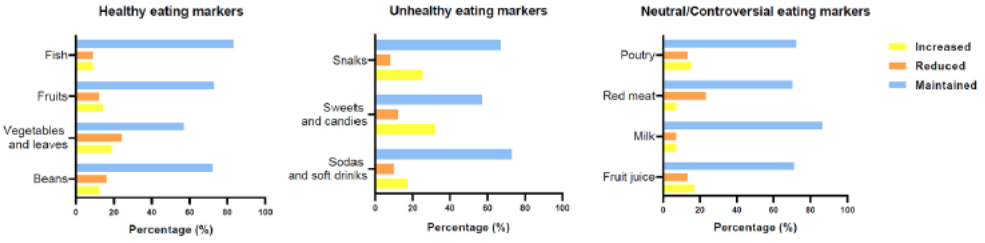

Fig. 1 Changes in the consumption of the food groups confronting the times before and during social distancing

were the less frequently practiced (6.9%). About half of the participants (49.4%) reported having increased their sitting times in front of the TV, computer, mobile, or other devices (49.1%).

Our regression models tested the associations between the dependent health variables and independent lifestyle variables during the SD. The simple models are detailed in the S4 Table, whereas the multiple regression models with diet components, physical exercises, and sedentary behavior are described in Tables S5 and S6. The final multiple models are presented in Table 4. The odds of presenting depressive symptoms from the crude models were increased by a poor sleep quality (OR = 2.00; p = 0.002), an increased sitting time in front of the TV (OR = 2.11; p = 0.001), or in front of the computer, mobile, or other devices (OR = 1.60; p = 0.037), and by income reduction (OR = 2.50; p < 0.001). The higher intake of fruit juices (OR = 0.52; p = 0.047) and the age (OR = 0.95; p < 0.001) decreased these odds (S4 Table). When data on dietary habits were included simultaneously in a multiple model (S5 Table), the odds of depressive symptoms were decreased with lower fruit juices intake (OR = 0.54; p = 0.043). In models including physical activity and sedentary behavior simultaneously (S6 Table), increased time in front of the TV enhanced (OR = 1.96; p = 0.01), and practicing physical exercises reduced the odds of depressive symptoms (OR = 0.64; p = 0.052). According to the final multiple models described in Table 4, increased time in front of the TV (OR = 1.90; p = 0.027) and poor sleep quality (OR = 1.98; p = 0.006) increased the odds of depressive symptoms; lower intake of fruit juices (OR = 0.54; p = 0.048) reduced these odds. When the sociodemographic variables were included in the model, the time in front of the TV (OR = 1.83; p = 0.044), the poor sleep quality (OR = 1.78; p = 0.027), and reduced income (OR = 2.11; p = 0.005) enhanced the odds of depressive symptoms, while the age reduced these odds (OR = 0.96; p = 0.006).

The odds of increasing the body weight from crude models (S4 Table) were augmented with lower vegetable intake (OR = 2.61; p = 0.001), poor sleep quality (OR = 1.76; p = 0.005), increased time in front of the TV (OR = 1.98; p = 0.001), in front of the computer, mobile or other devices (OR = 2.08; p = 0.001) and with the reduction in income (OR = 1.84; p = 0.003). Low intake of sweets and candies (OR = 0.61; p = 0.04), low intake of snacks replacing meals (OR = 0.41; p = 0.001), and higher age (OR = 0.95; p < 0.001) reduced these odds. Multiple analyses including all food components (S5 Table) showed that the low intake of vegetables (OR = 2.96; p = 0.001) enhanced the odds of increasing body weight, while the low intake of poultries (OR = 0.57; p = 0.02) and the low intake of snacks replacing meals (OR = 0.54; p = 0.037) reduced these odds. The models that included physical activity and sedentary behavior simultaneously (S6 Table) pointed out that higher time in front of the computer, mobile, or other devices increased the odds of augmenting the body weight (OR = 1.71; p = 0.03). From the final multiple models (Table 4), the odds of increasing body weight were augmented with low vegetable intake (OR = 2.77; p = 0.002); when the sociodemographic variables were included in the model, whereas low intake of vegetables still increased (OR = 3.00; p = 0.001), the age reduced (OR = 0.95; p = 0.001) these odds.

The odds of self-perceiving health as regular, bad, or very bad from the crude models (S4 Table) were augmented with poor sleep quality (OR = 3.20; p < 0.001), with increased time in front of the TV (OR = 2.64; p < 0.001), in front of the computer, mobile or other devices (OR = 1.94; p = 0.004), with high intake of sweets and candies (OR = 1.72; p = 0.046), and with the reduced income (OR = 1.66; p = 0.029). Practicing physical exercises (OR = 0.30; p < 0.001), higher milk intake (OR = 0.50; p = 0.033), low intake of snacks replacing meals (OR = 0.54; p = 0.02), and older age (OR = 0.97; p = 0.006) reduced these odds. The model with all food components (S5 Table) showed that the self-perceived health as regular, bad, or very bad was reduced with high milk intake (OR = 0.48; p = 0.037). From the models with physical activity and sedentary behavior (S6 Table), the odds were increased with higher time in front of the TV (OR = 2.05; p = 0.01) and reduced with practicing physical exercises (OR = 0.31; p < 0.001). From the final multiple models (Table 4), the odds of regular, bad, or very bad self-perception of health were increased with time in front of the TV (OR = 1.95; p = 0.025) and with poor sleep quality (OR = 2.50; p < 0.001); practicing physical exercises (OR = 0.36; p < 0.001) reduced these odds. The inclusion of sociodemographic variables in the model showed that physical exercises (OR = 0.33; p < 0.001) and older age (OR = 0.97; p = 0.027) reduced the odds of a regular, bad, or very bad self-perception of health; the time in front of the TV (OR = 1.90; p = 0.032) and the poor sleep quality (OR = 2.46; p = 0.001) increased these odds.

We performed some nuanced analyses on the groups that possibly were more affected by the pandemic (subgroup considering only the women and subgroup considering only the persons at the lower formal schooling classification). S7 Table presents the description and changes in our primary outcome (depressive symptoms, body weight changes, and self-perception of health) according to our nuanced analyses. Depressive symptoms more than doubled (+42.52% and +39.88% for females and people with the lower formal schooling, respectively), similar to the whole sample (+42.1%). Regarding the regular, bad, or very bad self-perception of health, women increased by 17.32%, and people with lower formal schooling increased by16.07% during SD; the whole sample increased by18.0%. Finally, 60.3% of the women and 51.79% of the people with lower formal

Table 4 Multiple models of logistic regression between the dependent variables (health) and independent (lifestyle and sociodemographic) variables during SD

		Unadjusted models						Adjusted Models[@]					
Independent variables		Depressive symptoms		Body weight changes		Perceived health status		Depressive symptoms		Body weight changes		Perceived health status	
	Categories	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Healthy eating markers#													
Beans	Low Intake	1.02 (0.58–1.80)	0.925	0.72 (0.43–1.23)	0.240	1.24 (0.70–2.19)	0.460	1.05 (0.58–1.88)	0.863	0.67 (0.39–1.17)	0.164	1.26 (0.71–2.26)	0.421
	High intake	1.27 (0.69–2.31)	0.432	0.83 (0.47–1.45)	0.517	0.79 (0.41–1.52)	0.494	1.47 (0.79–2.75)	0.216	0.85 (0.48–1.52)	0.598	0.81 (0.42–1.59)	0.553
Vegetables and leaves (raw)	Low Intake	1.37 (0.67–2.77)	0.380	2.77 (1.44–5.30)	0.002	0.96 (0.50–1.85)	0.921	1.32 (0.63–2.75)	0.449	3.00 (1.53–5.85)	0.001	0.96 (0.49–1.86)	0.908
	High intake	1.18 (0.66–2.11)	0.569	1.48 (0.85–2.56)	0.161	0.69 (0.36–1.31)	0.266	1.21 (0.67–2.21)	0.513	1.49 (0.85–2.61)	0.163	0.71 (0.37–1.35)	0.302
Vegetables and leaves (cooked)	Low Intake	0.95 (0.50–1.81)	0.888	0.97 (0.54–1.74)	0.929	1.29 (0.69–2.40)	0.423	0.97 (0.50–1.89)	0.936	0.91 (0.50–1.65)	0.759	1.23 (0.65–2.32)	0.513
	High intake	0.72 (0.39–1.33)	0.298	1.15 (0.63–2.08)	0.633	1.65 (0.83–3.28)	0.149	0.66 (0.35–1.23)	0.195	1.01 (0.55–1.85)	0.956	1.61 (0.81–3.22)	0.172
Fish	Low Intake	1.50 (0.58–3.85)	0.392	1.80 (0.74–4.35)	0.190	0.71 (0.25–1.98)	0.523	1.53 (0.58–3.97)	0.382	1.72 (0.71–4.19)	0.228	0.66 (0.24–1.82)	0.431
	High intake	0.29 (0.01–4.39)	0.375	0.42 (0.02–6.42)	0.539	--	--	0.14 (0.00–2.69)	0.196	0.27 (0.01–4.64)	0.369	--	--
Fruits	Low Intake	1.57 (0.74–3.33)	0.239	1.25 (0.64–2.42)	0.500	0.84 (0.42–1.67)	0.637	1.63 (0.75–3.55)	0.212	1.23 (0.62–2.41)	0.547	0.83 (0.41–1.66)	0.610
	High intake	0.62 (0.35–1.11)	0.110	0.90 (0.52–1.54)	0.708	0.96 (0.52–1.77)	0.905	0.72 (0.39–1.31)	0.288	1.03 (0.59–1.80)	0.904	1.06 (0.57–1.99)	0.839
Unhealthy eating markers#													
Sodas and soft drinks	Low Intake	1.15 (0.61–2.19)	0.649	1.04 (0.58–1.88)	0.883	1.30 (0.68–2.47)	0.416	1.14 (0.59–2.19)	0.693	1.04 (0.56–1.91)	0.890	1.30 (0.68–2.49)	0.414
	High intake	1.63 (0.65–4.10)	0.295	0.90 (0.40–2.01)	0.806	2.19 (0.94–4.81)	0.070	1.73 (0.66–4.49)	0.260	0.83 (0.36–1.89)	0.668	2.19 (0.96–5.03)	0.062
Sweets and candies	Low Intake	1.09 (0.62–1.92)	0.756	0.64 (0.38–1.07)	0.092	1.14 (0.62–2.08)	0.664	1.11 (0.62–1.99)	0.722	0.64 (0.37–1.09)	0.103	1.25 (0.68–2.32)	0.461
	High intake	0.86 (0.46–1.58)	0.631	1.59 (0.88–2.85)	0.119	1.30 (0.69–2.45)	0.404	0.88 (0.46–1.67)	0.704	1.67 (0.91–3.04)	0.092	1.40 (0.73–2.66)	0.302
Snaks replaced a meal	Low Intake	1.22 (0.66–2.26)	0.522	0.59 (0.32–1.06)	0.078	0.74 (0.41–1.35)	0.339	1.33 (0.70–2.52)	0.379	0.61 (0.33–1.12)	0.112	0.76 (0.41–1.40)	0.388
	High intake	2.06 (0.56–7.50)	0.271	1.04 (0.32–3.34)	0.944	1.59 (0.52–4.87)	0.410	1.95 (0.52–7.37)	0.320	1.04 (0.30–3.59)	0.942	1.62 (0.51–5.13)	0.411
Neutral or controversial eating markers#													

Table 4 (continued)

		Unadjusted models						Adjusted Models[@]					
Red meat	Low Intake	0.94 (0.56–1.57)	0.815	0.65 (0.40–1.06)	0.089	1.06 (0.61– 1.82)	0.828	0.90 (0.53–1.53)	0.702	0.63 (0.39–1.04)	0.076	1.03 (0.59–1.79)	0.894
	High intake	0.93 (0.44–1.96)	0.858	1.12 (0.54–2.30)	0.749	1.10 (0.49–2.47)	0.806	0.92 (0.43–1.98)	0.842	1.12 (0.53–2.35)	0.755	1.04 (0.46–2.37)	0.916
Poultry	Low Intake	0.78 (0.47–1.30)	0.348	0.62 (0.38–1.01)	0.055	0.90 (0.53–1.55)	0.730	0.81 (0.48–1.37)	0.450	0.67 (0.41–1.09)	0.113	0.93 (0.54–1.60)	0.802
	High intake	1.05 (0.44–2.46)	0.904	0.83 (0.38–1.83)	0.657	1.01 (0.42–2.44)	0.976	0.98 (0.41–2.37)	0.979	0.86 (0.39–1.89)	0.714	1.02 (0.42–2.48)	0.953
Fruit juice	Low Intake	0.54 (0.29–0.99)	0.048	0.84 (0.48–1.45)	0.536	1.61 (0.86–3.00)	0.129	0.55 (0.29–1.04)	0.066	0.89 (0.50–1.57)	0.690	1.59 (0.85–2.97)	0.144
	High intake	0.61 (0.29–1.25)	0.179	0.98 (0.50–1.91)	0.964	0.81 (0.35–1.83)	0.618	0.67 (0.32–1.39)	0.286	1.10 (0.56–2.19)	0.768	0.82 (0.36–1.87)	0.641
Milk	Low Intake	0.59 (0.26–1.32)	0.202	0.78 (0.39–1.56)	0.486	0.66 (0.32–1.36)	0.266	0.63 (0.28–1.45)	0.285	0.86 (0.42–1.78)	0.703	0.70 (0.33–1.45)	0.341
	High intake	0.62 (0.28–1.37)	0.242	0.68 (0.34–1.37)	0.291	0.59 (0.29–1.22)	0.161	0.66 (0.29–1.47)	0.312	0.73 (0.36–1.50)	0.403	0.64 (0.31–1.33)	0.235
Sleep quality	Poor	1.98 (1.22–3.23)	0.006	1.52 (0.97–2.39)	0.066	2.50 (1.49–4.20)	0.000	1.78 (1.06–2.98)	0.027	1.34 (0.84–2.16)	0.215	2.46 (1.45–4.19)	0.001
	Good (ref.)	1		1		1		1		1		1	
Physical exercise practice	Yes	0.76 (0.46–1.25)	0.286	1.07 (0.67–1.71)	0.757	0.36 (0.21–0.63)	0.000	0.67 (0.40–1.13)	0.138	0.97 (0.60–1.56)	0.903	0.33 (0.19–0.59)	0.000
	No (ref.)	1		1		1		1		1		1	
Sitting time in front of the TV	Increased	1.90 (1.07–3.35)	0.027	1.45 (0.85–2.46)	0.168	1.95 (1.08–3.50)	0.025	1.83 (1.01–3.32)	0.044	1.41 (0.81–2.43)	0.213	1.90 (1.05–3.43)	0.032
	Reduced	2.20 (0.73–6.61)	0.158	1.12 (0.44–2.88)	0.803	0.83 (0.24–2.80)	0.768	1.98 (0.62–6.28)	0.244	0.98 (0.36–2.61)	0.971	0.74 (0.21–2.54)	0.633
	No change (ref.)	1		1		1		1		1		1	
Sitting time in front of cell phone and other devices	Increased	0.95 (0.52–1.72)	0.876	1.39 (0.80–2.40)	0.238	1.12 (0.60–2.07)	0.707	0.82 (0.44–1.55)	0.560	1.36 (0.77–2.40)	0.285	1.03 (0.55–1.93)	0.905
	Reduced	1.07 (0.37–3.07)	0.886	1.13 (0.45–2.82)	0.789	1.20 (0.44–3.28)	0.717	0.93 (0.31–2.80)	0.907	1.06 (0.41–2.75)	0.894	1.07 (0.38–2.98)	0.896
	No change (ref.)	1		1		1		1		1		1	
Sex	Male							1.47 (0.85–2.53)	0.163	0.67 (0.41–1.12)	0.134	1.15 (0.66–2.03)	0.604
	Female (ref.)							1		1		1	
Age (years)								0.96 (0.93–0.98)	0.006	0.95 (0.93–0.98)	0.001	0.97 (0.94–0.99)	0.027
Changes in income	Reduced							2.11 (1.25–3.55)	0.005	1.39 (0.87–2.22)	0.166	1.18 (0.70–1.98)	0.516
	Mantained or increased(ref.)							1		1		1	

Table 4 (continued)

	Unadjusted models	Adjusted Models[@]

#Low Intake = 0–2 days/week; moderate intake = 3–4 days/week; High intake = 5 or more days/week (moderate intake is the reference category for all the diet questions); [@]Model including sex, age and changes in the income during SD

schooling referred to increasing their body weight during SD; this percentage was 56.9% in the whole sample.

We could not run the multiple regression models; the number of cases for the three outcomes (presence of depressive symptoms, body weight changes, and self-perception of health) was not sufficient to reach the required degrees of freedom number in the models [25]. Thus, we just tested the single models. In S8 Table, we demonstrate the single regression models between the outcomes and independent variables in the female group. The odds of depressive symptoms increased by sitting time in front of the TV (OR = 3.37; p = 0.003) and the reduced income (OR = 2.92; p = 0.006). The older ages reduced these odds (OR = 0.94; p = 0.042). Regarding changes in body weight, these odds were increased by low fish intake (OR = 6.24; p = 0.026), sitting time in front of the cell phone, computer, and other devices (OR = 2.78; p = 0.010), reduced income (OR = 2.12; p = 0.043), and lower formal schooling (OR = 2.20; p = 0.039); being older decreased these odds (OR = 0.94; p = 0.022). Finally, low fruits and poultry intake (OR = 4.10; p = 0.024 and OR = 3.14; p = 0.020, respectively), high soft drinks intake (OR = 5.50; p = 0.013), poor sleep quality (OR = 3.31; p = 0.011) and sitting time in front the TV (OR = 2.61; p = 0.021) increased the odds of having a poor self-perception of health; the higher milk intake (OR = 0.29; p = 0.033) and practicing physical exercises (OR = 0.35; p = 0.017) reduced these odds.

S9 Table depicts the single regression models between the dependent and independent variables in the lower formal schooling group. The presence of depressive symptoms had the odds increased by poor sleep quality (OR = 2.83; p = 0.003), sitting time in front of the TV, and in front of a cell phone, computer, and other devices (OR = 2.94; p = 0.004 and OR = 2.14; p = 0.042, respectively) and by the decreased income (OR = 2.95; p = 0.003); the older age reduced these odds (OR = 0.93; p = 0.006). The increase in body weight had the odds increased by low intake of vegetables (OR = 3.16; p = 0.014) and sitting time in front of the TV and in front of the cell phone, computer, and other devices (OR = 1.92; p = 0.043 and OR = 2.67; p = 0.003, respectively); being older decreased these odds (OR = 0.92; p = 0.001). The intake of cooked vegetables (OR = 2.26; p = 0.041), the poor sleep quality (OR = 4.18; p < 0.001), the sitting time in front of the TV and front of cell phones, computers, and other devices (OR = 2.27; p = 0.019 and OR = 2.97; p = 0.006 respectively) increased the odds of the poor self-perception of health; in turn, the low intake of snacks replacing meals (OR = 0.39; p = 0.031) and practicing physical exercise (OR = 0.27; p = 0.001) reduced these odds.

Discussion

We investigated changes in lifestyle of PLWH during COVID-19 SD and associated outcomes. Study participants, mainly well-educated and employed men aged over 50 years, reduced their income during SD. They followed SD correctly, and only a small proportion was infected by COVID-19, with few hospitalizations. Although most participants did not modify their diet, those who changed it reduced the intake of healthy eating markers and increased the ingestion of unhealthy ones. Most of the sample referred that their sleep quality worsened during SD. More than half did not practice physical exercises, and about half increased sedentary behavior. The negative self-evaluation of health increased twice during SD, whose odds increased by the sedentary behavior and poor sleep quality; otherwise, physical exercises reduced these odds. Most participants increased their body weight during SD, an outcome independently associated with the low intake of vegetables. Finally, depressive symptoms doubled during SD compared to previously, and this outcome had the odds enhanced by sedentary behavior, poor sleep quality, and reduced income. Interestingly, being older was associated with lower odds of the three outcomes investigated. Our nuanced analyses pointed to similar trends, but being female increased the strength of associations in the single regression models, particularly dietary intake (by higher odds ratio values).

Many published studies in 2020 with non-HIV participants have shown discordant results regarding lifestyle during SD. While in the NutriNet-France study [26] 56.2% of the participants reported a low intake of fresh and healthy foods, in NutriNet-Quebec (Canada) [27], the participants improved the quality of food intake during the early lockdown. Likewise, the NutriNet-Brasil study28 [28] showed that the consumption of healthy eating markers (i.e., vegetables, fruits, beans, and other legumes) increased, and the ingestion of unhealthy dietary markers (i.e., ultra-processed foods) did not change. Finally, an international survey conducted in several countries [12] found higher unhealthy food intake during home confinement. Similar to our results, these authors pointed to higher snack intakes during this period.

We planned our study based on many physiological assumptions. The first one was that the higher intake of healthy eating markers and the lower intake of unhealthy ones would be favorably associated with the study outcomes (depressive symptoms, body weight, and self-perception of health) [29, 30]. In fact, our results yielded some significant associations in our crude regression models, but most of these were not maintained when other independent variables were included in the models. The only exception was the association between body weight and vegetable intake; this association is in accordance with various studies that have shown beneficial components in vegetables, such as fiber, antioxidants, and anti-inflammatory [29]. Anywise, it is relevant to consider the long-term consequences of unhealthy changes in dietary intake during the SD.

Information about sitting time was one of the most outstanding findings in our results. Recent studies have highlighted differences between time in a sedentary state and physical inactivity or low level of physical activity. Sitting time is a state of very reduced energy expenditure and, when combined with stressful mental activities, can create glucose instability with significant physiological consequences. Therefore, sedentary behavior deserves special attention concerning long-term metabolic and mental disorders [31], which will assume greater relevance with the unique sedentary lifestyle imposed by COVID-19 SD; therefore, long-term consequences are yet to be disclosed.

Previous studies have shown associations between sedentary behavior, sleep quality, depressive symptoms, and poor health [31–33]. Thus, we can assume that all these variables created by the uncertainties caused by the pandemic constitute a network of interactions. We observed a simultaneous and independent association between sedentary behavior and low sleep quality, increasing the odds of depressive symptoms and lousy self-perception of health. Previous cross-sectional studies showed, for instance, that internet addiction and poor sleep quality coexist and increase the odds of depressive symptoms [34, 35]. It is essential to highlight that poor sleep quality is a common issue in PLWH, independently of the SD [36].

Apart from the pandemic, chronic conditions and diseases are frequent in PLWH, which are associated with low-grade systemic inflammation (LGSI) [37–39]. The LGSI occurs because of a residual viral action and many side effects of prolonged antiretroviral therapy [40, 41]. Besides the increased cardiovascular risk caused by this inflammatory condition, circulating inflammatory molecules can cross the blood-brain barrier, increasing neuroinflammation and modifying neurotransmitter syntheses, such as melatonin and serotonin. The altered neurotransmitter profile impacts the likelihood of mental health burden, with higher rates of stress and anxiety, and can be a risk factor for developing HIV-associated neurological disorders (HAND) [42, 43]. Therefore, considering the role of lifestyle in managing LGSI and chronic conditions, our results highlight the urgent need for interventions to prevent a future burden of health commitment in this population group [44].

Besides physiological and metabolic issues in the post-COVID-19 moments, the socioeconomic burden has emerged as a worrisome aspect. Cross-sectionally, our sample showed significant associations between reduction in income and the presence of depressive symptoms, verified

in other surveys worldwide, with non-HIV-infected persons [45]. It is essential to highlight that the socioeconomic impact of the pandemic varies significantly in different areas of the globe; particularly in Brazil, evident economic inequalities that existed in pre-pandemic times have aggravated with COVID-19, which leads to very bleak expectations [46]. It is fundamental to address inequities in health for specific groups, and in this context, PLWH will need a particular agenda.

An unexpected finding of our study was that older age reduced the odds of the three investigated outcomes, which is discordant with the physiological assumptions we used and with recent publications. For instance, Plagg et al. [47] called attention to the fact that loneliness and social isolation experienced by older adults during COVID-19 may undermine their resilience. Other authors state that multiple comorbidities increase vulnerability to unfavorable outcomes during the pandemic [48, 49]. Based on our data, we hypothesize that the PLWH may have developed mechanisms to improve their resilience or ability to cope with stressful situations.

It is essential, at this point, to mention some limitations of our sample that can impede extrapolating this discussion to other groups of PLWH. Our research setting follows many patients living in more affluent areas of Sao Paulo City, and their privileged social conditions, such as high schooling and employment, could help them deal with the pandemic times. Also, assuming that older sample participants could be receiving the clinic's multidisciplinary follow-up for a long time could explain our analyses' particular findings. Another limitation is our cross-sectional design, which impairs the assumption of causality. Conversely, our findings still raise worrisome concerns about the impact of COVID-19 SD on PLWH and the need to have their long-term consequences carefully followed up and managed. In addition, to our knowledge, this is the first study investigating specifically the dietary habits of PLWH during COVID-19 SD.

In conclusion, we demonstrated relevant changes in lifestyle in PLWH during COVID-19-imposed SD that showed associations with depressive symptoms, body weight, and self-perception of health. These results call attention to the need to carefully follow these population groups to avoid the accumulation of personal and health system burdens.

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Authors' contributions BMV, JVN, MVLSQ and CMM participated in the collection, analyses, and interpretation of the data; RB, ECMS, CMP, KYI, VIAS, ACS participated in the writing and reviewing of the final version; SMLR supervised the project and participated in all steps of the work.

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Data Availability All the supporting data are presented as Supplementary files. Additional information may be obtained upon written request to the corresponding author.

Declarations

Conflict of interest and Source of Funding All the authors declare no conflicts of interest.

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Consent to participate All the study's participants signed an informed consent about the research.

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Artigo 4 - Association between sleep quality and lifestyle factors in persons living with HIV during the COVID-19 social distancing: a web-based survey. Submetido à revista Sleep Health e negado. Atualmente está em ajuste para nova submissão.

Association between sleep quality and lifestyle factors in persons living with HIV during the COVID-19 social distancing: a web-based survey

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Abstract

We aimed to verify the effect of diet and physical activity changes on the sleep quality of PLWH during COVID-19 SD. This is a secondary study of a broader cross-sectional survey. Patients registered at an HIV/AIDS clinic in São Paulo answered a web-based questionnaire including sleep quality (categorized by good or poor sleep quality) and sleep duration (categorized by short ≤ 6h, normal 7-8 h or long ≥ 9h sleep duration). Lifestyle questions included diet, physical activity, and sedentary behavior. The associations were tested by binominal and multinomial logistic regressions models. A total of 405 PLWH (279 men, 127 women), mean age 50.7 years, responded to the questionnaire. The variables which showed increased odds of poor sleep quality were lower intake of cooked vegetables (OR, 1.78; 95% CI, 1.01 to 314; p= 0.045), increased time in front of cell phone and other devices (OR, 1.80; 95% CI, 1.05 to 3.10; p= 0.032), and decrease family income (OR, 2.16; 95% CI, 1.39 to 3.35; p= 0.001). In turn, physical exercise reduced these odds (OR, 0.51; 95% CI, 0.31 to 0.85; p= 0.010). Unhealthy dietary practices showed unfavorable association with sleep quality, whilst physical exercise practice improved the sleep. These results highlight the need of a pos-pandemic strategies to ameliorate PLWH lifestyle related-factors.

Keywords: COVID-19 social distancing; persons living with HIV; dietary practices; physical exercise, sedentary behavior, sleep quality.

Introduction

Since the beginning of COVID-19 pandemic, it has been demanded strategies to reduce the virus spread, such as social distancing (SD), masks use, and mainly the vaccination [1]. Due to the absence of effective treatment and the slow pace of the vaccination especially in low- and middle-income countries, the SD remains necessary. Despite favourable regarding viral transmissibility, SD can lead to complex and significant behavioral and psychological consequences [2-4]. Several studies published during the COVID-19 SD showed that in general, persons showed, in comparison to the times before pandemic, lower dietary quality and reduced level of physical activity, together with changes in sleep quality and increased presence of mental disorders [5-9].

These issues possibly deserve especial attention in persons living with HIV (PLWH). The life trajectory of this population group puts them at increased risk because they have already experienced or perceived the stigma that impairs the formation of social networks [10]. PLWH are more likely to live alone, have few friends, and are more socially dissatisfied [11]. Recently, Nguyen et al. [12] conducted an internet-based, cross-sectional survey to verify the impact of COVID-19 SD on PLWH well-being. Participants reported that SD impacted their lives "much" (22%), "very much" (44%) or "extremely" (18%); they also referred changes in sleep pattern (54%). Apart from COVID-19, sleep problems in PLWH are identified by studies conducted in different parts of the World [13-16] and has been found associations between these problems and immune system disturbances and side-effects of antiretroviral therapy. It is estimated that between 40 to 70% of PLWH had poor sleep quality, and several HIV-related factors can explain sleep problems [17-19].

The association between lifestyle factors such as diet and physical activity with sleep has been increasingly studied [20-22]. In brief, Western dietary patterns and sedentary behavior are associated with poor sleep quality, while Mediterranean dietary patterns and regular physical exercise practice are positive associated with better sleep quality [23-28]. In turn, there is a lack of studies investigating this type of association in PLWH, particularly during the COVID-19 SD. As such, we aimed to explore changes in dietary intake and lifestyle-related parameters with the sleep quality of PLWH during COVID-19 social distance.

Methods

The present study is secondary from broader research that investigated multiple health parameters of PLWH during COVID-19 SD. It is a web-based cross-sectional survey, conducted from November 2020 to January 2021, with a convenience sample from an HIV/AIDS specialized clinic in São Paulo linked to Hospital das Clinicas of the University of Sao Paulo Medical School (SEAP-HCFMUSP). A virtual questionnaire was completed by the participants using a web application Google Forms®. The questionnaire included multiple-choice questions concerning sociodemographic, lifestyle and health information during COVID-19 SD. The local Ethics Committee approved this study (protocol 4.285.897).

Sleep quality and sleep duration

The following questions investigated the sleep parameter. How do you consider your sleep? Possible responses were very good, good, regular, poor, and very poor sleep quality. Sleep duration was verified by a subjective question related to sleep duration: "How many hours do you sleep a night?" The possible answers about sleep quality were: “Very good“, “good“, “Regular“, “poor, or “very poor“. For the analyses, the groups were merged in two categories: “very good“/ “good“ and “poor” and “very poor“ for “poor sleep quality“. Sleep duration was described in hours and interpreted in three categories: [short (≤6 h/night), average (7-8 h/night) or long (≥ 9h/night) sleep duration)].

Diet questions

The questions about diet were chosen and adapted from a nationwide health survey carried out by the Ministry of Health in partnership with the Brazilian Institute of Geography and Statistics (IBGE) [29]. We organized two sets of questions. The first set comprised healthy eating markers (raw and cooked vegetables and whole fruits), and the second set comprised unhealthy ones (soft drinks, sweets and candies, and snacks replacing meals) [30, 31]. These questions referred to the period during the SD, being the weekly frequency of each set of eating markers classified in three categories: low intake (once to twice a week); moderate (3 to 4 times) and high intake (5 or more times).

Sedentary behavior and Physical exercise practice

The sedentary behavior (sitting time in front of the TV and sitting time using a cell phone or other devices) was reported if increased, maintained, or reduced comparing the period

before and during social distancing. Moreover, the participants answered the question "Are you exercising during social distancing"?

Sociodemographic variables

The questionnaire included information on age (reported in years), sex (male, female, or other), and changes in family income during the SD (reduced, increased, or maintained).

Statistical Analysis

Normality of the data were tested by the Kolmogorov-Smirnov test. Categorical data are presented as frequencies/proportions, and the continuous as mean and standard deviation. Binomial (sleep quality as dependent variable) and multinomial (sleep duration as dependent variable) logistic regression models were performed to investigate the association between sleep parameters and the independent variables. For both types of regression models, the analyses followed the steps: (i) Crude models were tested against all the independent variables (food groups intake, sedentary behavior, physical exercise practice, family income, sex, and age); (ii) Multiple Model 1: simultaneous inclusion of food groups intake, sedentary behavior and physical exercise practice; (iii) Multiple Model 2: included, together with Model 1, the sociodemographic variables family income, sex, and age. All the missing data were disregarded for the statistical analyses. Statistical significance adopted for the regressions models was 5%, and analysis was performed in Stata version 14 (Stata Corp College Station), USA.

Results

Table 1 depicts the sample characteristic. A total of 406 PLWH (68.7% men, mean age 50.7 years) took part in the survey; 58.5% referred to high education level. During SD, the percentage of participants who decreased or maintained their family income during COVID-19 SD was 49.7% and 45.3%, respectively. Besides, most of the participants related worsened sleep quality (54.4%) and shorter sleep duration (43.9%). With respect to food intake, raw (39.9%) and cooked (47.3%) vegetable were moderately ingested (3-4 days/week); soft drinks (65.3%) and sweets (37.9%) intake were predominantly low; most participants (73.6%) increased the intake of snacks in replacement of meals. Almost half of the participants (49.5%) increased the time in front of the TV, and in front of cell phones and other devices (49.1%). Also, 57.2% reported not practicing any type of exercise at home during SD.

Table 2 and Supplementary table 1 describe the binomial regression models taking sleep quality as dependent variable. From the significant associations found in crude models (fruits and vegetables increasing odds of good sleep quality; sodas and soft drinks and snacks replacing meals increasing the odds of poor sleep quality; increasing sitting time in from the TV, cell phone and other devices increasing the odds of poor sleep quality and changing the sleep duration; reduced family income worsening the sleep quality; age modifying the sleep duration), only few of them were maintained in the multiple models. In all the models, the low intake of cooked vegetables increased the odds of having poor sleep quality (p=0.019, 0.046 and 0.045 for crude, multiples models 1 and 2 respectively); the same was observed with regard to increased sitting time in front of cell phone and other devices (p=0.003, 0.036 and 0.001 for crude, multiples models 1 and 2 respectively). In crude model and in multiple model 2, the inclusion of sociodemographic variables showed the reduced income to increase the odds of poor sleep quality (p=0.001 for both models). On other hand, practicing physical exercise during SD reduced the odds of having poor sleep quality (p=0.002, 0.011 and 0.01 for crude, multiples models 1 and 2 respectively). Regarding the sleep duration, only the age showed significant odds of long sleep duration in multiple model 2 (p= 0.037).

Supplementary table 2 describe multinomial regression models taking sleep duration as dependent variable. The crude models showed significant association between sleep duration and sedentary behavior [increased time in front of TV and reduced time in front of cell phone and other devices (OR=0.82; p=0.006 and OR=1.22; p=0.018 respectively, both associations with sleeping time ≥9h/night)] and age (OR=0.03; p=0.010 against sleeping time ≥9h/night). However, in multiple adjusted models, only the age was maintained as significant (0.03; p=0.037 against sleeping time ≥9h/night).

Discussion

We explored the association between lifestyle variables (nutrition, sedentary behavior, and physical exercise practice) and sleep quality and duration. The majority of the sample related poor sleep quality during SD. Regarding lifestyle, our most worrisome variables were the increased sedentary behaviour and the low percentage of the participants who practised physical exercises during SD; in turn, the dietary practices did not change expressively during SD. Even so, the lower intake of vegetables and the sedentary behaviour were significantly associated with poor sleep quality, and physical exercise practice decreased these odds.

We assessed some food groups previously described to be linked with sleep quality [30, 31],[32-35]. Our results showed that a low intake of vegetables increased the odds for poor sleep quality, but not for sleep duration. Likewise, Jansen et al. [36] in showed non-HIV sample, that fruit and vegetable intake was significantly associated with better sleep quality. Noorwali et al. [30] verified that low (<7 h) or high (>8 h) sleep duration were not significantly associated with vegetable intake.

Sleep is a critical factor for control metabolic and inflammatory status [37], and insufficient sleep quality, duration, or efficiency are associated with several harmful conditions, diseases, and mortality, mainly by cardiovascular disease [38, 39]. The relationship between sleep and diet was previously reported, and mechanisms that explain the role of nutrients on sleep are diverse; however, the nutrient-mediated inflammatory process emerges as the central pathway that explains how nutrition could modulate sleep [24, 40, 41]. Poor sleep quality impairs the immune system, decreasing immune cell activation, proliferation and differentiation [42, 43], and affect neuronal transmission by modifying the expression of neurotransmitters and their receptors [44]. Moreover, poor sleep quality or short duration were previously associated with weight gain, altered blood lipids, insulin resistance, and cardiovascular diseases [45-49]. The PLWH, especially the older ones, have a higher risk of developing several metabolic disturbances and diseases due to the residual effect of the virus and antiretroviral therapy (ART) [50]. Both promote persistent immune activation and low-grade chronic systemic inflammation (LGCSI) [51].

In general, studies that evaluated COVID-19 SD on dietary intake of PLWH are scarce, although the concern about PLWH food insecurity during the COVID-19 pandemic has already been reported [52]. Even in non-HIV persons, few studies have associated dietary practices with sleep during COVID-19 SD. Ramos-Padilla et al. [21] verified aspects related to food and sleep but did not perform association analyses. Martinez-de-Quel et al. [53] found worsening of sleep, physical activity, and quality of life during SD but did not see changes in eating behavior.

We observed that sedentary behaviour (measured by the time in front of TV, cell phone and other devices) were significantly associated with sleep quality; otherwise, practicing physical decreased these odds. Physical exercise with moderate intensity seems to be favorable to sleep quality [26, 27], and better sleep quality could be more beneficial for daily live activities, creating a positive vicious cycle. Different physiological and metabolic aspects could

explain these associations, such as low inflammatory status and high levels of brain-derived neurotrophic factor created by the exercise, energy expenditure, body core temperature regulation, decreased microglia activation, among others [25, 54]. Furthermore, spending more time on a cell phone may be related to poor sleep quality because it affects the melatonin kinetic [55]. Nowadays, the cell phone is widely used due for social media (for leisure and work), what was previously associated with poor sleep quality when in excess [56].

Several studies showed that physical activity levels reduced during COVID-19 SD [28, 57]. For instance, some persons decreased transport and leisure time, while others stopped physical exercise practices, or did both. This behavior is derived from home working, studying, and passing the time in boredom moments. However, it is not clear if the low physical activity level is a cause or consequence of poor sleep quality. Heiland et al. [58] assessed moderate-to-vigorous physical activity, sedentary behaviour and sleep time or efficiency, and showed a bi-directional relationship between more sedentary behavior during daytime and short sleep duration. Besides, it was observed that moderate-to-vigorous physical activity was not associated with sleep, suggesting that low physical activity levels result from insufficient sleep-related parameters.

Moreover, we verified that low family income was associated with high odds of poor sleep quality. Corroborating to our findings, Bedaso et al. [16] verified, in PLWH, that insufficient social support and the lowest monthly income were associated with poor sleep quality in Ethiopia. Concerns with lost employment, home-related problems, food acquisition, medicines, health treatments, acquire the virus, fear, and death could explain, at least in part, the negative effect of COVID-19 SD on sleep by raising the psychological distress [59-61].

Our study has some limitations, such as (i) cross-sectional design that does not allow assuming causality; (ii) sleep quality and duration were assessed by subjective perception. On the other hand, as far as we know, our study was the first to verify the effect of COVID-19 SD on PLWH lifestyle-related parameters and sleep quality. Although our data were collected in November 2020 and January 2021, recent comparisons showed that the frequency of lifestyle-related parameters (i.e., exercise practice and soda, snacks, vegetables, and fruit intake, etc.) was not changed between April 2020 and November 2020, reinforcing the persistent effect of COVID-19 SD on daily life practices [62].

Conclusion

Unhealthy dietary practices showed unfavorable association with sleep quality, whilst physical exercise practice improved the sleep. These results highlight the need of a pos-pandemic strategies to ameliorate the habits of these persons.

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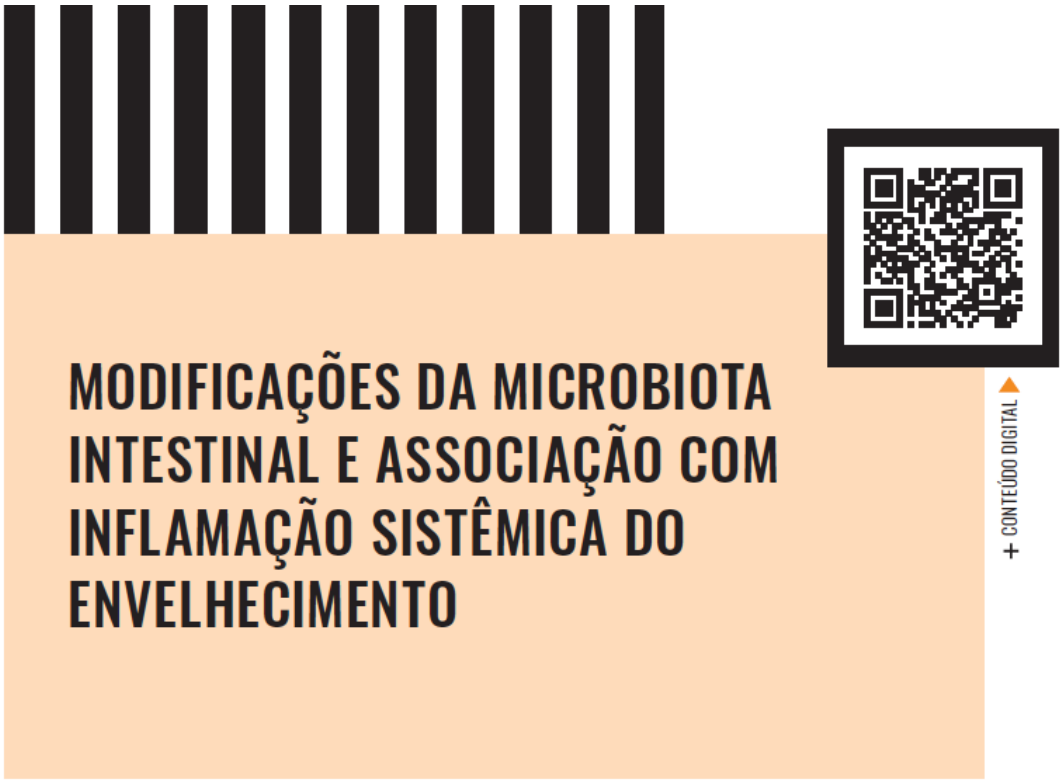
Capítulo de Livro – Modificações da Microbiota Intestinal e Associação com Inflamação Sistêmica do Envelhecimento. Publicado – Programa de Atualização em Nutrição Clínica: Ciclo 10 / Organizado pela Associação Brasileira de Nutrição.

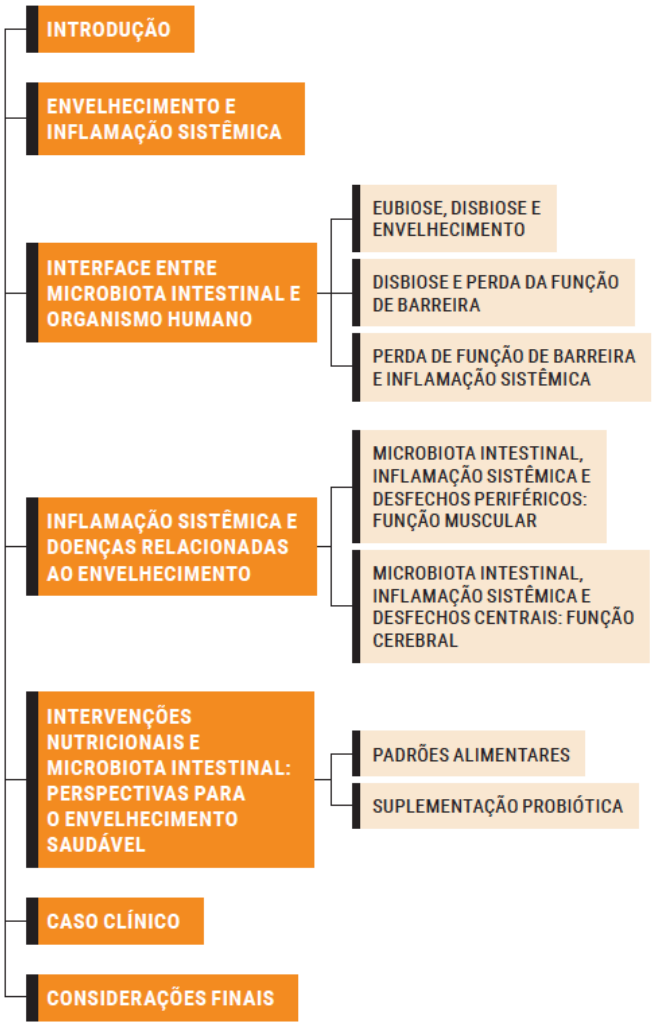


// Marcus Vinicius Lucio Dos Santos Quaresma // Camila Guazzelli Marques // Sandra Maria Lima Ribeiro

OBJETIVOS

Ao final da leitura deste capítulo, o leitor será capaz de

- reconhecer as mudanças na microbiota intestinal (MI) decorrentes do envelhecimento;
- identificar a relação entre as alterações da MI e a inflamação sistêmica;
- listar repercussões musculares e cerebrais da alteração da MI no processo de envelhecimento.


INTRODUÇÃO
ENVELHECIMENTO E INFLAMAÇÃO SISTÊMICA
INTERFACE ENTRE MICROBIOTA INTESTINAL E ORGANISMO HUMANO
EUBIOSE, DISBIOSE E ENVELHECIMENTO
DISBIOSE E PERDA DA FUNÇÃO DE BARREIRA
PERDA DE FUNÇÃO DE BARREIRA E INFLAMAÇÃO SISTÊMICA
INFLAMAÇÃO SISTÊMICA E DOENÇAS RELACIONADAS AO ENVELHECIMENTO
MICROBIOTA INTESTINAL, INFLAMAÇÃO SISTÊMICA E DESFECHOS PERIFÉRICOS: FUNÇÃO MUSCULAR
MICROBIOTA INTESTINAL, INFLAMAÇÃO SISTÊMICA E DESFECHOS CENTRAIS: FUNÇÃO CEREBRAL
INTERVENÇÕES NUTRICIONAIS E MICROBIOTA INTESTINAL: PERSPECTIVAS PARA O ENVELHECIMENTO SAUDÁVEL
PADRÕES ALIMENTARES
SUPLEMENTAÇÃO PROBIÓTICA
CASO CLÍNICO
CONSIDERAÇÕES FINAIS

INTRODUÇÃO

Em 2012, a primeira publicação completa sobre a identificação do microbioma humano permitiu ampliar a compreensão, de forma integrada, do organismo humano.[1] A existência de diferentes microecossistemas em diversas partes do corpo humano tem direcionado milhares de estudos, que continuam identificando relações com a saúde e o risco de doenças. Esses achados foram e têm sido possíveis graças a tecnologias de sequenciamento genético e ao desenvolvimento da bioinformática, que permitem a identificação de diferentes escalas taxonômicas dos microrganismos residentes, bem como a proporcionalidade entre eles, suas funções e especificidades.[2]

A partir do estudo do microbioma humano, a MI vem ganhando destaque na comunidade científica e na prática clínica. Entre as informações obtidas pelos estudos com a MI, está a constatação de modificações com o envelhecimento. Essas alterações têm repercussões imunes e metabólicas, que parecem se associar com grande parte das doenças e dos comprometimentos relacionados à velhice. Assim, considerando o aumento da longevidade humana, compreender mecanismos capazes de melhorar a saúde dessa população é fundamental.

Neste capítulo, será discutida a estreita relação entre nutrição e MI, sobretudo como essa relação tem permitido o delineamento de estratégias alimentares, na perspectiva de contribuir para um envelhecimento saudável.

ENVELHECIMENTO E INFLAMAÇÃO SISTÊMICA

O processo de envelhecimento é plural, complexo e influenciado por uma matriz de fatores que interatuam. Trata-se de um fenômeno biopsicossocial e, portanto, sua qualidade envolve uma combinação de fatores genéticos e ambientais.[3] Os fatores ambientais incluem o estilo de vida; logo, uma dieta variada, prática de atividade física e ambientes seguros diminuem o risco de doenças e, assim, aumentam a saúde e a longevidade.[3,4]

Com o envelhecimento, ocorre uma série de alterações metabólicas e fisiológicas, que incluem alterações da composição corporal, comprometimento cognitivo, doenças crônicas, entre outras. Essas alterações estão atreladas a mudanças em funções endócrinas, nervosas e imunes, com repercussões metabólicas.[5] Nesse quadro, merece destaque o **envelhecimento do sistema imune** ou **imunossenescência**.[5]

O envelhecimento do sistema, ou imunossenescência, consiste na perda ou em modificações de funções de praticamente todas as suas células e dos produtos celulares.

Exemplos de mudanças causadas pela imunossenescência incluem as seguintes:

- o tamanho do timo diminui, resultando em menor resposta e novos estímulos;
- as células adaptativas, de memória, reduzem a capacidade de reconhecer novos antígenos;
- o metabolismo energético de células, como os neutrófilos, impede a diapedese para locais de infecção, e as células apresentadoras de antígenos diminuem a capacidade de fagocitose.

Por outro lado, células apresentadoras de antígenos, especialmente os macrófagos, tornam-se hiperestimuladas, secretando uma quantidade acima do normal de moléculas inflamatórias (citocinas) na circulação sanguínea, como a interleucina-6 (IL-6) e o fator de necrose tumoral-α (TNF-α), por exemplo. Essa concentração aumentada de moléculas inflamatórias na circulação foi denominada por Franceschi e colaboradores[6] de ***inflammaging***.

Estudos recentes que buscaram compreender os mecanismos relacionados ao *inflammaging* identificaram, além da própria imunossenescência, **fatores imunoativadores**, como os seguintes:

- redução na habilidade celular de remover resíduos;
- aumento e redistribuição da gordura corporal;
- alterações na MI.

Neste capítulo, o foco será a MI, por isso serão discutidas a sua estrutura e as suas funções, bem como as interações com o funcionamento do corpo humano e com o envelhecimento.

INTERFACE ENTRE MICROBIOTA INTESTINAL E ORGANISMO HUMANO

Os principais componentes do ecossistema intestinal são:

- a MI;
- uma dupla camada de muco;
- as células epiteliais;
- o sistema imune próprio do intestino (em inglês, *gut-associated lymphoid tissue* [GALT]).

MICROBIOTA INTESTINAL

A MI é comumente reconhecida como uma diversa e densa comunidade de microrganismos, incluindo diferentes arqueias, alguns eucarióticos e, principalmente, bactérias.[7]

Os **intestinos delgado e grosso** apresentam as maiores concentrações bacterianas, girando em torno de 108 a 109 e de 1.011 a 1.014 bactérias/g de tecido, respectivamente.[7–9]

Os principais estudos sobre as categorias filogenéticas residentes na MI identificaram, até o momento, a presença de cerca de 10 filos bacterianos. Todavia, a maioria (cerca de 90%) se concentra em dois deles:

- Bacteroidetes — abrangem gêneros de bactérias Gram-negativas, como ~~as~~ *Bacteroides*, *Prevotella*;
- Firmicutes —abrangem gêneros Gram-positivos, como *Clostridium*, *Faecalibacterium*, *Lactobacillus*, *Ruminococcus* e *Roseburia*.

Outros filos em menor proporção, como *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia* e *Fusobacteria*, também compõem a MI.[8,10,11]

Apesar da maior proporcionalidade de Bacteroidetes e Firmicutes, os demais filos também apresentam importância à saúde humana. Por exemplo, acredita-se que o filo Fusobacteria, embora pouco conhecido, desempenhe papel essencial na gênese de diversas condições patológicas.[8,10,11] Da mesma maneira, o filo Verrucomicrobia, que inclui a espécie bacteriana *Akkermansia muciniphila*, tem demonstrado funções importantes no cólon e no metabolismo, ainda que represente apenas 0,5 a 5% do total de bactérias da MI.[12] Além disso, tem sido identificado que o papel individual de certas bactérias é fundamental no desenvolvimento de algumas doenças.[10]

DUPLA CAMADA DE MUCO

A **camada de muco** desempenha função de **defesa física**, impedindo que os microrganismos interajam diretamente com o epitélio intestinal. O muco também serve de substrato energético para diversas famílias de bactérias, como *Clostridiaceae*, *Akkermansiaceae*, *Bifidobacteriaceae* e *Bacteroidaceae*.

Exemplos das bactérias dessas famílias que metabolizam a mucina na MI incluem as seguintes:[13]

- *Akkermansia muciniphila*;
- *Bacteroides fragilis*;
- *Bacteroides vulgatus*;
- *Bifidobacterium* spp.;
- *Prevotella* spp.

Células epiteliais intestinais

As **células epiteliais intestinais (CEIs)** são representadas, principalmente, por enterócitos, células de Paneth (produtoras de peptídeos antibacterianos) e células Goblet (ou caliciformes, que secretam muco). Essas células também se encontram intercaladas com células enteroendócrinas (produtoras de hormônios gastrintestinais) e células M (que são parte do sistema imune do intestino). A interação entre as CEIs e a MI permite a mediação de mecanismos de regulação das alterações que ocorrem no intestino.[14–16]

Para as CEIs exercerem adequadamente sua função de barreira à entrada de invasores, é fundamental que estejam fortemente unidas célula a célula.[17] A adesão entre as células adjacentes é regulada por complexos juncionais intracelulares, que consistem em proteínas de junções estreitas (*tight junctions*), junções aderentes, junções comunicantes e desmossomos.[17]

SISTEMA IMUNE PRÓPRIO DO INTESTINO

O **GALT** é imprescindível no **reconhecimento de patógenos e outros invasores** e, por consequência, na **resposta imune**.[18] Inclui, principalmente, as placas de Peyer e as criptas (aglomerados de células do sistema imune, sobretudo linfócitos T e B), além de folículos linfoides isolados.[18,19] As placas de Peyer contêm, na sua superfície, células epiteliais especializadas conhecidas como células M.

As **células M** se localizam intercaladas com as CEIs e formam "bolsos" que permitem, por exemplo, a captação de antígenos para posterior internalização na placa e fagocitose pelas células dendríticas para posteriores apresentação aos linfócitos-T e ativação dos linfócitos-B.[18] Ainda, na cúpula subepitelial, estão presentes as células dendríticas, diversas populações de linfócitos T $CD4^+$ de memória, linfócitos B e imunoglobulinas (Ig) A, M e G.[18]

No ecossistema intestinal, ocorrem trocas benéficas entre os microrganismos residentes e o hospedeiro. De um lado, as bactérias encontram um ambiente favorável para residirem e extraírem as substâncias necessárias para sua manutenção. Em troca, elas auxiliam o corpo humano na proteção contra invasores, produzindo nutrientes e metabólitos. Esses nutrientes e metabólitos, além de permitirem a manutenção da camada de muco (função trófica), colaboram na sinalização de vias pró- e anti-inflamatórias (função imune) e contribuem com o fornecimento de alguns nutrientes essenciais para a saúde (função nutricional).[18]

Produção de metabólitos

Destacam-se os **metabólitos** produzidos a partir da fermentação de carboidratos não digeríveis, sobretudo fibras dietéticas (polissacarídeos), ou carboidratos acessíveis à microbiota (CAMs), como os seguintes:[20]

- amido resistente;
- β-glucanos;
- frutoligossacarídeos (FOSs);
- mucilagem;
- pectina.

A fermentação realizada pelas bactérias da MI deve-se, sobretudo, a enzimas como as CAZy, que não existem nas células intestinais humanas. Essas enzimas são hidrolases que podem quebrar as ligações glicosídicas dos CAMs. Os produtos dessa ação enzimática são, principalmente, os ácidos graxos de cadeia curta (AGCCs): o acetato, o butirato e o propionato.[20]

No cólon, os AGCCs favorecem a homeostase da mucosa intestinal principalmente por meio de efeitos diretos nas CEIs e nas células imunológicas da lâmina própria.[20] Em particular, o butirato aumenta a função de barreira, regulando a expressão das proteínas responsáveis pela ligação estreita entre os enterócitos (*tight junctions*) por meio da ativação da 5' proteína quinase ativada por adenosina monofosfato (em inglês, *adenosine monophosphate-activated protein kinase* [AMPK]) ou pela regulação negativa da expressão de claudina-2.[21] Além disso, os AGCCs, sobretudo o butirato e o acetato, também afetam a produção de muco no trato gastrointestinal.[21]

Além de exercerem efeitos locais no cólon, os AGCCs alcançam a circulação sanguínea sistêmica e participam de vias imunológicas, endócrinas e vagais.[20,21] No cérebro, por exemplo:[21]

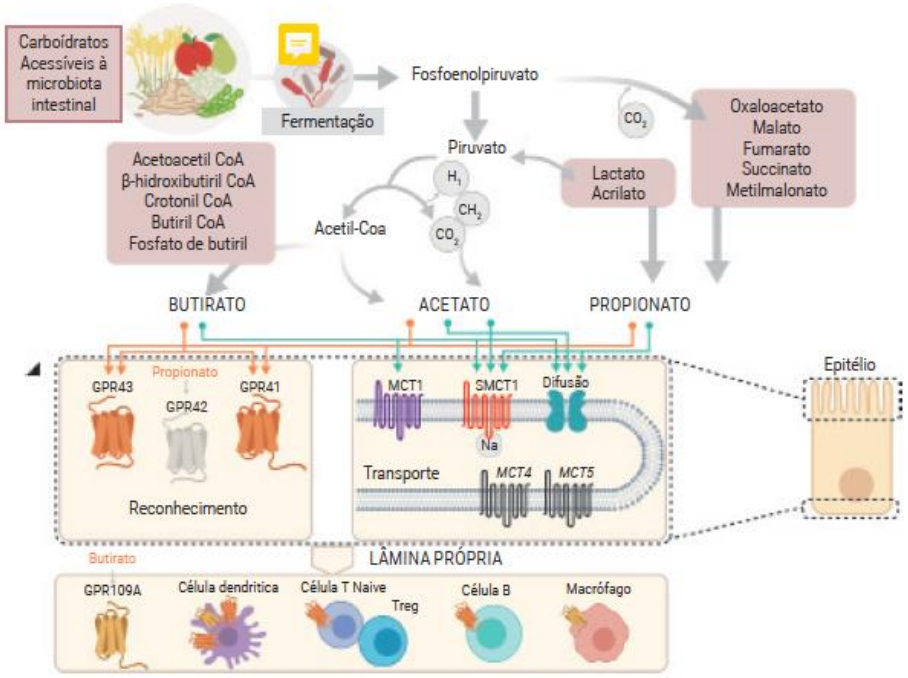
- afetam a morfologia e a função das células da micróglia;
- reforçam a integridade da barreira hematoencefálica;
- modulam a neurotransmissão;
- influenciam os níveis de fatores neurotróficos;
- contribuem para a biossíntese da serotonina.

LEMBRAR

Os receptores para AGCCs também são expressos no tecido adiposo branco, no fígado e na musculatura esquelética, indicando uma ação direta sobre o metabolismo energético humano.[22]

Além disso, pela via endócrina, os AGCCs induzem a **secreção de hormônios intestinais**, como o peptídeo semelhante ao glucagon-1 (GLP-1) e o peptídeo YY (PYY).[21] Ademais, o acetato, o propionato e o butirato podem diminuir diretamente a secreção de quimiocinas e citocinas pró-inflamatórias derivadas do tecido adiposo branco, modulando a inflamação sistêmica.[22] Portanto, evidências vêm demonstrando que os AGCCs desempenham funções determinantes na saúde humana.

A Figura 1 ilustra as etapas para produção dos AGCCs e suas interações. Os CAMs sofrem quebra e são metabolizados (fermentação) a fosfoenolpiruvato (PEP) e, em seguida, piruvato (PIR). Ambos, PEP e PIR, dão origem a produtos obtidos a partir de uma série de oxidações até formar os AGCCs. Os transportadores MCT1 e SMCT1 absorvem os AGCCs do lúmen, e MCT4 e MCT5 absorvem os AGCCs da membrana basolateral para fora da célula. Os receptores dos AGCCs GPCR43 e 41 são expressos em CEIs e células imunológicas específicas na lâmina própria e no tecido linfoide da mucosa, conforme indicado.[20]



CAMs: carboidratos acessíveis à microbiota intestinal; PEP: fosfoenolpiruvato; PIR: piruvato.

FIGURA 1: Metabolismo mediado por bactérias intestinais responsável pela produção dos AGCCs e as suas interações com receptores específicos presentes em diversas células. *// Fonte: Adaptada de van der Hee e Wells (2021).*[10]

EUBIOSE, DISBIOSE E ENVELHECIMENTO

Para que a coexistência entre a MI e o hospedeiro fosse possível — e considerando que o sistema imune humano está desenvolvido e adaptado para "combater" moléculas e organismos estranhos (considerados "antígenos") —, algumas adaptações foram necessárias. O GALT é capaz de desencadear processos que variam de **tolerância**, que permite a coexistência com a MI, até **inflamação**, quando ocorre a entrada de substâncias ou microrganismos estranhos que escapam à vigilância da MI residente.

Em situações de equilíbrio bacteriano, chamado de **eubiose**, a MI previne a colonização de substâncias ou organismos (patógenos) estranhos por meio de disputa física de espaços, principalmente na camada de muco, e pela produção de metabólitos que sinalizam o GALT. Ainda nas situações de eubiose, a coexistência recém-descrita também permite a presença simultânea, na luz intestinal da MI, de peptídeos antibacterianos produzidos pelas CEIs e de um anticorpo específico do hospedeiro, o **IgA**. Essas moléculas são importantes para ampliar o sistema de vigilância contra invasores.

Alguns fatores podem alterar a eubiose; por exemplo, alterações na dieta (dieta baixa em carboidratos fermentáveis e elevada em componentes potencialmente inflamatórios) e no padrão de atividade física são os principais fatores relacionados ao estilo de vida. Além disso, o uso de determinados medicamentos, algumas doenças e o processo de envelhecimento podem provocar alterações desfavoráveis à MI, levando à condição de **disbiose**.[2]

[criterios de diagnóstico] Na disbiose, três características principais de uma MI saudável são alteradas: a diversidade, a estabilidade e a resiliência. Assim, a identificação de disbioses deve ser antecedida pela análise do perfil da MI, pelo estabelecimento de alguns índices de diversidade e pelo aumento da densidade de bactérias potencialmente patogênicas. Sintomas como alterações anormais do trânsito intestinal podem indicar a necessidade de investigações mais aprofundadas.[2]

Diversos estudos têm identificado a elevada ocorrência de disbiose com o envelhecimento. O envelhecimento provoca mudanças na diversidade da MI, marcadas, principalmente, pela redução de bactérias que produzem os AGCCs, como *Bifidobacterium*, e pelo aumento de gêneros de bactérias potencialmente patogênicas, como *Clostridium*, *Lactobacillus*, *Enterobacteriaceae* e *Enterococcus*.

Ainda, estudos recentes observaram reduções, com o envelhecimento, de gêneros bacterianos associados a marcadores benéficos à saúde, como *Christensenella*, *Akkermansia* e *Bifidobacterium*. O interessante é que esses três gêneros estão presente em maior abundância em centenários e supercentenários, sugerindo efeitos favoráveis à longevidade.[13,23,24]

Outros estudos associaram o envelhecimento a um aumento de bactérias patogênicas, como *Escherichia/Shigella* e *Proteobacteria*, acompanhado de redução de outras comensais, como *Faecalibacterium*.[13,23,24]

LEMBRAR

Recentemente, Galkin e colaboradores[25] propuseram a classificação da MI de idosos como senopositivas ou senonegativas, com base no papel das bactérias intestinais sobre senescência. Os autores consideraram o gênero *Bifidobacterium* senonegativo, isto é, benéfico. Por outro lado, o *Clostridium*, em razão dos efeitos neurotóxicos, foi considerado senopositivo, por interferir negativamente na senescência.[25]

Wilmanski e colaboradores[26] verificaram, em idosos (idade superior a 78 anos) aparentemente saudáveis, que apenas o gênero *Bacteroides* foi reduzido com a idade. Os idosos que não preenchiam critérios para serem considerados saudáveis apresentaram menor abundância relativa dos gêneros *Lachnoclostridium* e *Rumminococace*. Segundo os autores, esses resultados indicam que pode haver diferentes padrões de MI ao longo do envelhecimento, os quais estão associados aos comprometimentos à saúde.[26]

No mesmo estudo, os pesquisadores verificaram associação positiva entre o gênero *Bacteroides* e a mortalidade, independentemente da idade, o índice de massa corporal (IMC) e a autopercepção de saúde. Em uma análise de subgrupos (apenas idosos com idade superior a 85 anos), os autores verificaram que a associação entre o gênero *Bacteroides* e a mortalidade fica mais forte.[26]

Além disso, o gênero *Bacteroides* consistiu em importante marcador do envelhecimento saudável, reforçando os achados de outros estudos que observaram que esse gênero aumenta à medida que a idade avança.[27] Contudo, idosos mais velhos (octogenários, nonagenários e centenários) apresentaram menor abundância desse gênero. Esses mesmos autores apontaram o aumento de metabólitos bacterianos como produtos da fermentação de fenilalanina e tirosina (*p*-cresol, sulfato, fenilacetilglutamina e *p*-cresol glucoronida), considerados xenobióticos (ou estranhos) ao envelhecimento.[26]

No Quadro 1, estão descritas algumas mudanças na MI associadas ao envelhecimento.

QUADRO 1

PRINCIPAIS FATORES ASSOCIADOS ÀS MUDANÇAS NA COMPOSIÇÃO DA MICROBIOTA INTESTINAL

FATORES ASSOCIADOS		BACTÉRIAS ENVOLVIDAS	POSSÍVEIS MECANISMOS
Fisiologia do intestino	Inflamação	■ *Bacteroidaceae* ■ *Erysipelotrichaceae*	■ Alteração redox ■ Modificações de "nichos" bacterianos em diferentes localizações do trato gastrintestinal ■ Disponibilidade de nutrientes
	Menor espessura de muco	■ *Clostridiaceae* ■ *Akkermansiaceae* ■ *Bi dobacteriaceae* ■ *Bacteroidaceae*	■ Redução de mucina e de nutrientes moduladores
	Imunossenescência	■ *Clostridiaceae* ■ *Bi dobacteriaceae* ■ *Lachnospiraceae* ■ *Coriobacteriaceae*	■ Redução da função de barreira ■ Redução da tolerância imune ■ Inflamação local
Condições de vida	Hospitalizações/ moradia	■ Diversidade dos metabólitos bacterianos (por exemplo, AGCCs) ■ *Lachnospiraceae* ■ *Rikenellaceae*	■ Mudança na diversidade alimentar, principalmente no conteúdo de CAMs ■ Oportunidade e capacidade de se exercitar ■ Comorbidades e medicação

PRINCIPAIS FATORES ASSOCIADOS ÀS MUDANÇAS NA COMPOSIÇÃO DA MICROBIOTA INTESTINAL

Estado de saúde	■ *Prevotellaceae* ■ *Bacteroidaceae* ■ *Lachnospiraceae* ■ *Venillonellacease* ■ *Rikenllaceae* ■ *Ruminococcaceae* ■ *Methanobacteriaceae* ■ *Eubacteriaceae* ■ *Enerobacteriaceae*	■ Mudanças fisiológicas atribuídas a condições de saúde ■ Medicamentos ■ Frequência de uso de antibióticos ■ Adaptações fisiológicas e imunes à fragilidade ■ Oportunidade e capacidade de se exercitar ■ Estresse socioemocional (preocupações financeiras e isolamento social) ■ Habilidade e acesso a uma dieta saudável

AGCCs: ácidos graxos de cadeia curta; CAMs: carboidratos acessíveis à microbiota intestinal. //
Fonte: Adaptado de DeJong e colaboradores (2020).[28]

DISBIOSE E PERDA DA FUNÇÃO DE BARREIRA

Uma importante consequência da disbiose é a quebra da função de barreira, com consequente resposta imune. Nessas situações, alguns fragmentos bacterianos, ao interagir com as regiões apical e basolateral das células epiteliais, ativam **respostas inflamatórias** e **vias intracelulares** que desregulam as proteínas de junções estreitas (*tight junctions*). Isso resulta no aumento da **permeabilidade intestinal**, permitindo a passagem de bactérias ou componentes bacterianos para a circulação sanguínea.[23,29,30]

Cabe, nesse contexto, destacar alguns aspectos relacionados ao próprio envelhecimento e à MI que contribuem para o aumento da permeabilidade intestinal.[31–33] O envelhecimento é marcado pela **redução de células-tronco pluripotentes** em todas as células do organismo, incluindo as CEIs, o que dificulta a renovação e a diferenciação celulares. Além disso, as alterações na MI e, por consequência, no sistema nervoso entérico reduzem a capacidade de renovação e diferenciação das CEIs por processos ainda não totalmente elucidados.[31–33]

Possivelmente, esses processos envolvem ações diretas ou indiretas dos metabólitos e dos neurotransmissores, como AGCCs, serotonina, glutamato e ácido gama-aminobutírico (GABA), e/ou gêneros bacterianos responsáveis pela produção desses metabólitos, como *Fusobacterium*, *Clostridium*, *Eubacterium* e *Faecalibacterium*.[32,33]

Além das alterações imunes provocadas pela disbiose intestinal, a imunossenescência atinge todas as células do GALT, o que causa maior estado inflamatório e, consequentemente, maior risco de permeabilidade intestinal. Ambos os processos (imunossenescência e alterações da MI) provocam um desequilíbrio entre linfócitos-T reguladores (anti-inflamatórios) e linfócitos-Th17 (inflamatórios), favorecendo um ambiente pró-inflamatório.

LEMBRAR

Acredita-se que, na velhice, haja maior abundância de bactérias intestinais efetoras da diferenciação de linfócitos-Th17, aumentando a liberação de citocinas inflamatórias (especialmente IL-17) e maximizando, assim, o estado inflamatório.[34]

PERDA DE FUNÇÃO DE BARREIRA E INFLAMAÇÃO SISTÊMICA

Como mencionado, a perda de função de barreira permite a passagem de bactérias e fragmentos bacterianos para a circulação sistêmica. O principal fragmento bacteriano que atinge a circulação é o **lipopolissacarídeo (LPS)**, que faz parte da parede celular de bactérias Gram-negativas (sobretudo do filo Firmicutes).[29]

O processo de passagem de inúmeras substâncias potencialmente patogênicas do intestino até a corrente sanguínea é conhecido como *leaky gut*.

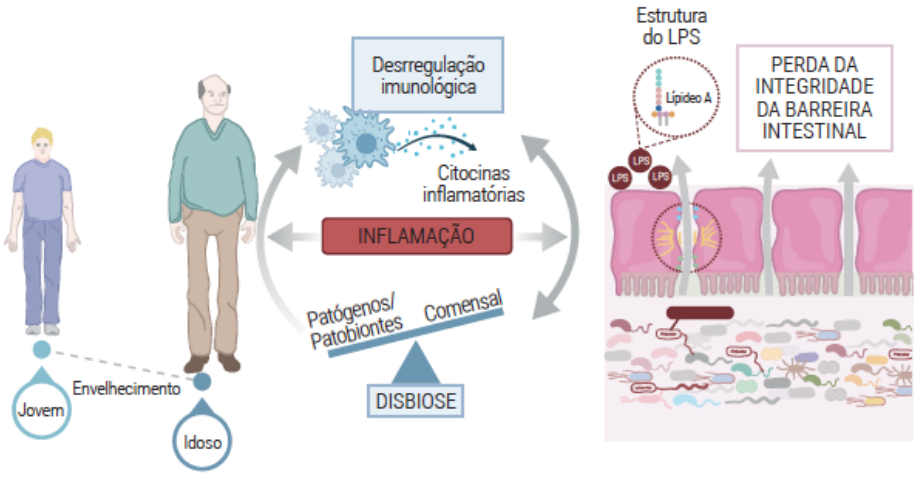
O *leaky gut* ocorre, principalmente, pelo **aumento da permeabilidade intestinal transcelular**, provocado pelo "afrouxamento" das proteínas de junções estreitas (*tight junctions*).

Em diferentes tecidos do organismo (incluindo as próprias células do sistema imune), o LPS se liga a receptores denominados **receptores semelhantes ao Toll** (em inglês, *Toll-like receptors* [TLRs]), dos quais se destaca o TLR-4.[29] A interação entre o LPS e o TLR-4 desencadeia sinais intracelulares que, entre outras consequências, podem

- ativar receptores nucleares que alimentam processos inflamatórios (indicados pelo aumento da concentração de citocinas inflamatórias na circulação);
- impedir a correta sinalização da insulina, resultando na redução da síntese de proteínas;
- ativar as vias de degradação proteica.

As moléculas com atividade imunológica que residem no intestino, quando na circulação, favorecem a inflamação sistêmica, que é a própria definição do *inflammaging*. Nesse contexto, é fundamental destacar que a relação entre a MI e *inflammaging* parece ser **bidirecional**, uma vez que o aumento do processo inflamatório prejudica a integridade da barreira intestinal.[33]

A Figura 2 ilustra a relação bidirecional entre a MI e o processo inflamatório.



LPS: lipopolissacarídeo; MI: microbiota intestinal.

FIGURA 2: Relação entre envelhecimento, MI e processo inflamatório. *// Fonte: Adaptada de Bana e Cabreiro (2019).*[33]

O fenótipo do envelhecimento e as doenças associadas à idade são promovidas por uma rede de processos biológicos que interagem em um ciclo de *feedback*. Inflamação sistêmica, disbiose intestinal, desregulação imunológica e perda da integridade da barreira intestinal são marcadores-chave do envelhecimento, estando, portanto, intrinsecamente interligadas. Em razão de seus efeitos interagirem, é difícil separá-los como determinantes singulares do envelhecimento, mas sua associação revela como o hospedeiro e a MI devem ser considerados ao desvendar os mecanismos do envelhecimento.[33]

ATIVIDADES

1. Com relação ao processo conhecido como *inflammaging*, assinale **V** (verdadeiro) ou **F** (falso).

___ Representa uma concentração diminuída de moléculas inflamatórias na circulação.

___ De maneira simplista, o termo *inflammaging* descreve o fenômeno representado pelo permanente estado inflamatório em que o idoso se encontra.

___ As origens do *inflammaging* no envelhecimento são diversas, incluindo a imunossenescência e mudanças na composição corporal (redução da massa muscular e aumento da adiposidade, por exemplo).

___ É marcado pela elevada concentração de citocinas inflamatórias.

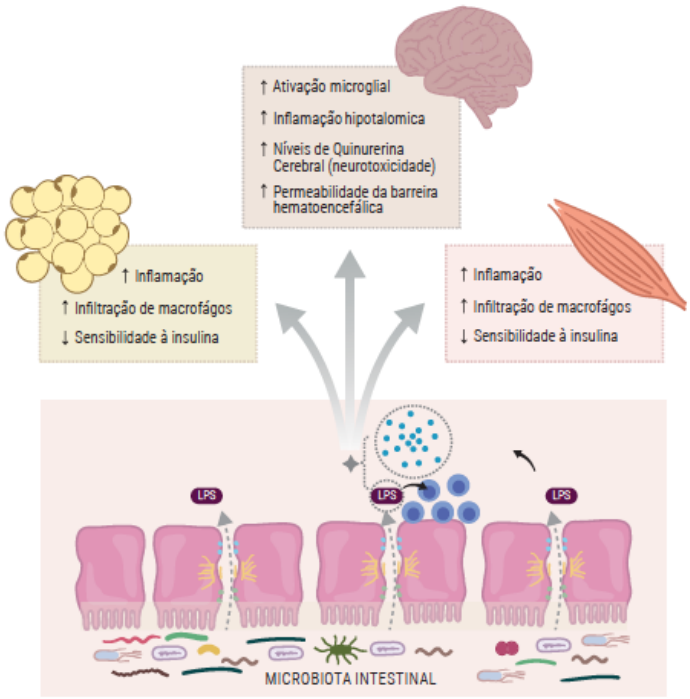
▼ Assinale a alternativa que apresenta a sequência correta. >> Resposta no final do capítulo

Ⓐ V – F – V – F
Ⓑ F – V – V – V
Ⓒ F – F – F – V
Ⓓ V – V – F – F

>> INFLAMAÇÃO SISTÊMICA E DOENÇAS RELACIONADAS AO ENVELHECIMENTO

As alterações na composição da MI e na produção de metabólitos, junto com o aumento da permeabilidade intestinal e a subsequente inflamação sistêmica, têm sido associadas a diversas doenças comuns no envelhecimento, como doenças crônicas (diabetes, hipertensão e doenças cardiovasculares), sarcopenia, fragilidade e doenças neurodegenerativas.[35,36]

Na Figura 3, estão ilustradas as relações entre permeabilidade intestinal, ativação imunológica, inflamação sistêmica e desfechos periféricos.



LPS: lipopolissacarídeo; MI: microbiota intestinal.

FIGURA 3: Aumento da permeabilidade intestinal, imunoativação, inflamação sistêmica e alterações periféricas. *// Fonte: Adaptada de Zheng e colaboradores (2020),[23] Odenwald e Turner (2017),[30] Li e colaboradores (2021).[37]*

O vazamento de fragmentos bacterianos (por exemplo, o LPS) induz à **imunoativação**, aumentando a circulação de citocinas inflamatórias que alcançam diversos tecidos, como o cerebral, o adiposo e a musculatura esquelética.[23,30,37]

MICROBIOTA INTESTINAL, INFLAMAÇÃO SISTÊMICA E DESFECHOS PERIFÉRICOS: FUNÇÃO MUSCULAR

Nos músculos esqueléticos, o LPS interage com o TLR-4, ativando o inflamassoma e, por consequência, fatores nucleares (como o NF-κB), que, por sua vez, aumentam a expressão gênica de citocinas inflamatórias. O **processo inflamatório intramuscular** causa **desregulação de vias de sinalização da insulina**, o que interfere na captação da glicose e na síntese proteica muscular. Essas alterações impactam a quantidade e a qualidade do tecido muscular esquelético.[37,38]

O aumento da lipólise do tecido adiposo em decorrência do aumento da inflamação também tem efeitos no tecido muscular, uma vez que o excedente de ácidos graxos livres é captado e internalizado nesse tecido (acúmulo ectópico de gordura). Tal acúmulo intramuscular de lipídios deflagra vias inflamatórias, aumentando a resistência à insulina e a ativação de proteínas das vias de degradação proteica muscular.

Com relação à associação entre tecido muscular esquelético e MI, Fielding e colaboradores[39] apontaram que os idosos com maior massa magra e melhor desempenho físico apresentaram maior abundância dos gêneros *Prevotella* e *Barnesiella* em comparação aos idosos menos funcionais.

Recentemente, Kang e colaboradores[40] analisaram a diversidade da MI de pessoas envelhecidas estratificando-as em dois grupos: aqueles com sarcopenia e os controle saudáveis. As pessoas com sarcopenia apresentaram **menor diversidade bacteriana** (avaliada pelo índice CHAO-1) em comparação ao grupo-controle.[40]

Na análise taxonômica, os autores observaram que o filo Firmicutes é menos abundante nas pessoas com sarcopenia (40,4%), comparativamente a um grupo-controle (54,4%). Ainda, os autores verificaram que a abundância relativa dos gêneros *Lachnospira*, *Fusicantenibacter*, *Roseburia*, *Eubacterium* e *Lachnoclostridium* foi menor no grupo com sarcopenia, enquanto a do *Lactobacillus* foi maior. É importante notar que todos esses gêneros que diminuíram são produtores de butirato.[40]

Nas análises de correlação, os autores verificaram que a abundância dos gêneros *Roseburia* e *Eubacterium* apresentou tendência de se correlacionar positivamente com a massa muscular, e os gêneros *Lachnospira*, *Eubacterium* e *Ruminococcus* se correlacionaram significativa e positivamente com a força muscular.[40]

Finalmente, na tentativa de compreender como as mudanças taxonômicas influenciam a sarcopenia, vias específicas foram analisadas. Resultados metagenômicos pró-inflamatórios foram observados nas pessoas com sarcopenia, com maior biossíntese do LPS.

Alterações na MI também se associaram à **síndrome da fragilidade**.[41] Lim e colaboradores[42] verificaram que o gênero *Bacteroides* é mais prevalente em pessoas que preenchem os critérios da síndrome da fragilidade comparativamente a pessoas não frágeis. Os autores também encontraram forte associação entre esse gênero bacteriano e mortalidade.[42]

Esses estudos contribuem para demonstrar a associação entre MI e metabolismo proteico muscular. Pode-se inferir que as alterações na MI de idosos, com consequentes aumento da inflamação sistêmica e redução dos metabólitos, minimizam a disponibilidade de aminoácidos para o músculo e, por consequência, reduzem a atividade de proteínas responsáveis pela síntese proteica muscular.[43]

As informações descritas levam à hipótese de que intervenções alimentares ou de suplementação nutricional podem reduzir a inflamação sistêmica, o comprometimento de síntese proteica muscular e o consequente desenvolvimento de sarcopenia.

MICROBIOTA INTESTINAL, INFLAMAÇÃO SISTÊMICA E DESFECHOS CENTRAIS: FUNÇÃO CEREBRAL

As doenças neurodegenerativas são mais prevalentes na velhice — as mais comuns são a **doença de Parkinson (DP)** e a **doença Alzheimer (DA)**.[36] Ambas são associadas a eventos como disfunção mitocondrial, excessiva produção de espécies reativas de oxigênio (EROS) e aumento da ativação da micróglia (neuroinflamação).[44] Hipóteses de que a presença da disbiose e o aumento da permeabilidade intestinal contribuem para o desenvolvimento dessas doenças neurodegenerativas têm sido levantadas.[44,45]

A DP é caracterizada pela degeneração de neurônios dopaminérgicos e pela agregação de formas da proteína neuronal α-sinucleína (αSyn).[36]

Na DA ocorrem o acúmulo de placas extraneuronais formadas pela proteína β-amiloide e a formação de emaranhados fibrilares intraneuronais compostos, principalmente, pela proteína tau hiperfosforilada.[44]

Na análise da MI de pessoas com DP comparativamente a pessoas saudáveis, verificou-se aumento dos gêneros *Enterobacteriaceae*, que apresentam fenótipo pró-inflamatório. Ao mesmo tempo, observou-se redução de microrganismos intestinais responsáveis pela liberação de mediadores anti-inflamatórios.[46] O interessante é que a MI desregulada também prejudica o efeito dos fármacos comumente prescritos para DP, por afetar a absorção do medicamento.[36,47]

Além disso, em modelos não humanos, Sampson e colaboradores[48] apontaram que cepas patogênicas de *Escherichia coli* são capazes de produzir proteína amiloide, levando ao acúmulo de αSyn no intestino e no cérebro. Isso posto, reconhece-se que a MI participa da gênese da DP por meio de diferentes mecanismos.[48]

Compartilhando mecanismos muito semelhantes, relacionados principalmente à neuroinflamação, a MI também participa da patogênese da DA. Em pessoas com essa condição, foram identificadas mudanças na diversidade bacteriana intestinal, com redução do filo Firmicutes e do gênero *Bifidobacterium,* acompanhada do aumento de Bacteroidetes e dos gêneros *Escherichia* e *Shigella.* Essas mudanças estão associadas ao aumento do estado inflamatório e ao acúmulo de proteínas amiloides no cérebro.[49] De fato, o acúmulo de proteína β-amiloide é considerado um dos marcadores para o desenvolvimento da DA.

INTERVENÇÕES NUTRICIONAIS E MICROBIOTA INTESTINAL: PERSPECTIVAS PARA O ENVELHECIMENTO SAUDÁVEL

A dieta é capaz de modificar a composição da MI, sua atividade e a produção de metabólitos. Embora grande parte dos estudos esteja sendo realizada com suplementações de substâncias pré ou probióticas, outros componentes dietéticos são capazes de influenciar a MI, como compostos fenólicos, tipo de proteínas, lipídios, entre ~~o~~outros, principalmente por mecanismos de modulação do estado inflamatório.

Considerando que a dieta consiste no fornecimento de diversos componentes simultaneamente, os padrões dietéticos devem ser ponderados. A seguir, serão descritos os principais e mais atuais achados acerca dos efeitos dos padrões alimentares, dos CAMs e da suplementação probiótica sobre parâmetros avaliados relacionados à MI.

PADRÕES ALIMENTARES

Padrões alimentares, como a dieta **do Mediterrâneo**, são extensamente estudados em razão de efeitos protetores contra diversas doenças, sobretudo doenças crônicas. De modo similar, padrões alimentares que priorizam quantidades adequadas de frutas, vegetais, alimentos proteicos com baixo teor de gordura, alimentos ricos em ácidos graxos poli-insaturados (AGPIs) e grãos integrais são associados à prevenção de diversas doenças. Por outro lado, padrões alimentares que priorizam o consumo de alimentos com potencial inflamatório, como aqueles proteicos ricos em gordura saturada, carne processada, alimentos ultraprocessados, excesso de sal e açúcar refinados, contribuem para o desenvolvimento de doenças.

> O padrão alimentar mediterrâneo tradicional é caracterizado por alto consumo de vegetais, frutas, leguminosas, castanhas e cereais (principalmente não refinados), por consumo moderado a alto de peixes, azeite extravirgem e laticínios (sobretudo queijo e iogurte) e por baixo consumo de carne vermelha e derivados. Ainda, caracteriza-se pelo consumo moderado de álcool, particularmente de vinho tinto, durante as refeições.[50]

Estudos vêm mostrando que a associação entre padrões alimentares e doenças têm a MI como mediador. Por exemplo, Shikany e colaboradores[51] avaliaram, em um delineamento transversal, o padrão alimentar de idosos. A partir de métodos estatísticos específicos, foram identificados dois padrões alimentares:[51]

- **ocidental** – constituído por carnes processadas, grãos refinados, batatas, ovos, doces e salgados;
- **prudente** – caracterizado pelo consumo de frutas, vegetais, oleaginosas, carnes de peixe, frango e peru.

Os autores verificaram que a família Victivallaceae e os gêneros *Cetobacterium*, *Clostridium*, *Faecalibacterium*, *Lachnospira*, *Paraprevotella* e *Veillonella*, táxons bacterianos relacionados prioritariamente a mecanismos anti-inflamatórios, associaram-se de forma positiva ao padrão prudente. Por outro lado, as famílias Mogibacteriaceae e Veillonellaceae e os gêneros *Alistipes*, *Anaerotruncus*, *CC-115*, *Collinsella*, *Coprobacillus*, *Desulfovibrio*, *Dorea*, *Eubacterium* e *Ruminococcus*, táxons relacionados a um fenótipo mais pró-inflamatório, associaram-se de forma positiva ao padrão ocidental. Esses resultados reforçam a responsividade da MI aos padrões alimentares em idosos.[51]

Recentemente, Ghosh e colaboradores[52] apontaram, no estudo NU-AGE, que, após 1 ano de adesão à dieta do Mediterrâneo, houve aumento da abundância de bactérias favoráveis ao perfil anti-inflamatório, como *Faecalibacterium prausnitzii*, *Roseburia*, *Bacteroides thetaiotaomicron*, *Prevotella copri* e *Anaerostipes hadrus*, as quais são consideradas produtoras de AGCCs e com propriedades anti-inflamatórias. Esse aumento foi associado de forma positiva a menores fragilidade e função cognitiva, mas negativamente associado a mediadores inflamatórios, incluído a proteína C-reativa e a IL-17.[53]

A espécie *Faecalibacterium prausnitzii*, aumentada em padrões alimentares ricos em CAMs, desponta como importante espécie responsiva aos padrões alimentares benéficos à saúde. No envelhecimento, pesquisas já identificaram associação negativa entre *Faecalibacterium prausnitzii* e fragilidade,[53] o que reforça sua importância.

Com base nas evidências disponíveis até o momento, especula-se que a chave para os efeitos fisiológicos de um prebiótico é a utilização seletiva pelos microrganismos hospedeiros e, por conseguinte, os produtos metabólicos produzidos.[54]

Os principais produtos metabólicos produzidos pela fermentação de carboidratos não digeríveis são os AGCCs.[54] Porém, é fundamental ressaltar que a quantidade e a proporção relativas de cada AGCCs são dependentes da composição da MI, do substrato e do tempo de trânsito intestinal.[21]

Em estudos realizados em modelo animal, o consumo aumentado de carboidratos não digeríveis minimiza a inflamação, a neuroinflamação e o declínio cognitivo.[55] Apesar da ausência de dados sobre a MI, recentes revisões sistemáticas e metanálises têm reforçado efeitos positivos das frutas, dos vegetais e das fibras dietéticas para saúde na velhice.[56] Logo, considerando as evidências mecanicistas e clínicas obtidas até o momento, é coerente incentivar o consumo de CAMs por idosos, principalmente pelos potenciais efeitos sobre a MI.

SUPLEMENTAÇÃO PROBIÓTICA

Na área da saúde, o termo **probiótico** foi utilizado pela primeira vez em 1974, passando por diversas mudanças conceituais até a definição atual, proposta pela Organização das Nações Unidas para a Alimentação e Agricultura/Organização Mundial da Saúde (OMS) em 2001.[57,58]

Atualmente, os probióticos representam "microrganismos vivos que, quando administrados em quantidades adequadas, conferem benefício à saúde do hospedeiro".[59]

Os probióticos são comumente comercializados em pó (sachês), cápsulas liofilizadas ou em produtos lácteos selecionados, como leite fermentado ou iogurte.[59] Entre os distintos mecanismos envolvidos em suas **funções efetoras**, destacam-se os seguintes:[57]

- imunomodulação;
- supressão de patógenos (antagonismo direto e indireto);
- redução do estresse fisiológico;
- melhora da função de barreira do epitélio intestinal e da composição da MI.

Considerando as inúmeras disfunções intestinais relatadas na velhice, o uso de probióticos é muito comum, sobretudo para **equilibrar o trânsito intestinal**, evitando diarreias e quadros de constipação.

Na última década, o incentivo para suplementação probiótica é justificado pelos potenciais efeitos na tolerabilidade de alimentos com alto potencial fermentativo (lácteos e farináceos), síntese de vitaminas e melhor digestão proteica.[60] Contudo, frente aos avanços científicos sobre a temática, compreende-se que a suplementação probiótica é complexa e deve ser proposta com cautela.

Os efeitos dos probióticos no organismo são altamente dependentes da composição da MI do indivíduo, de modo que as respostas obtidas pelo consumo da mesma bactéria ou combinação de bactérias pode ser diferente entre as pessoas. Os questionamentos atuais, portanto, incluem os seguintes:

- como saber qual bactéria/cepa é adequada para cada condição patológica?
- como ponderar os efeitos positivos e negativos sem conhecer a MI residente pré-suplementação?
- quais parâmetros clínicos podem ser considerados para identificar responsas positivas ou negativas frente à suplementação probiótica?

Estudos do grupo dos autores deste capítulo foram pioneiros no uso de probióticos e FOSs para idosos, tendo sido verificada melhora do estado de hidratação e do funcionamento intestinal.[61,62] Estudos semelhantes observaram que a suplementação de *B. animalis lactis* com FOSs atenuou mediadores inflamatórios e alterações intestinais em idosos.[63] De fato, recente metanálise confirmou que a suplementação probiótica reduziu a incidência e a gravidade de infecções do trato respiratório superior.[64]

Além disso, pesquisas recentes apontaram que a suplementação probiótica (*L. plantarum*, *L. acidophilus* e L. reuteri) foi capaz de diminuir a prevalência de síndrome metabólica, fatores de risco cardiovascular e marcadores de resistência à insulina em idosos.[65] Isoladamente, a suplementação de *L. reuteri* melhorou parâmetros metabólicos relacionados à densidade mineral óssea de mulheres idosas. Outras pesquisas sugerem que *L. rhamnosus* GG pode evitar alterações negativas em marcadores do metabolismo da glicose e melhorar o desempenho cognitivo de idosos com a cognição comprometida.[66,67]

Cancello e colaboradores[68] verificaram que a suplementação de oito espécies (*S. thermophilus*, *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*) combinada à dieta mediterrânea hipocalórica (–250 kcal) aumentou a quantidade de *Akkermansia muciniphila* em mulheres idosas obesas.

LEMBRAR

A *Akkermansia muciniphila* tem sido amplamente estudada por ser uma bactéria degradadora de muco mais abundante em centenários e por parecer ser uma espécie marcadora de bom estado de saúde.[68]

Estudos disponíveis testaram diversas cepas (que têm demonstrado especificidades de acordo com a doença ou o acometimento), em quantidades (geralmente múltiplas de bilhões de unidades formadoras de colônias [10^9 UFC]) e tempos variados (entre semanas e meses), isoladas ou combinadas, sobre os mais diversos desfechos em saúde. Logo, os dados ainda são heterogêneos acerca da melhor cepa ou combinação de cepas, do tempo de suplementação e das quantidades adequadas.

Da mesma maneira, muitas dúvidas restam sobre qual seria a assinatura bacteriana mais ou menos responsiva às cepas testadas. Também se questiona, finalmente, se os efeitos dos probióticos, em uníssono a boas práticas alimentares, seriam igualmente relevantes. Por enquanto, as respostas a essas perguntas continuam em aberto no que concerne à suplementação probiótica em idosos.

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Outras atividades acadêmicas relacionadas ao Doutorado

International Conference on Frailty & Sarcopenia Research

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Certificate of attendance

This is to testify that

Marcus Quaresma

participated in the

12th International SCWD Conference on Cachexia, Sarcopenia and Muscle Wasting

Belin, Germany, 06/12/2019 - 08/12/2019

Stefan D. Anker

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SOCIETY ON SARCOPENIA, CACHEXIA AND WASTING DISORDERS

XIV Curso Avançado de Patogênese do HIV