

UNIVERSIDADE FEDERAL DE UBERLÂNDIA
INSTITUTO DE CIÊNCIAS BIOMÉDICAS
Programa de Pós-Graduação em Imunologia e Parasitologia Aplicadas

**O IMPACTO DA ALERGIA E DO EXERCÍCIO FÍSICO NA EFETIVIDADE DA
VACINA CONTRA SARS-CoV-2 EM INDIVÍDUOS VACINADOS PARA COVID-19**

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Uberlândia
Junho, 2024

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VACINA CONTRA SARS-CoV-2 EM INDIVÍDUOS VACINADOS PARA COVID-19**

Tese apresentada ao Colegiado do Programa de Pós-graduação em Imunologia e Parasitologia Aplicadas como requisito parcial para obtenção do título de Doutora em Imunologia e Parasitologia Aplicadas.

Discente: Laura Alves Ribeiro Oliveira

Orientador: Prof. Dr. Ernesto Akio Taketomi (ICBIM/UFU)

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RESUMO

A COVID-19, causada pelo SARS-CoV-2 e inicialmente identificada em 2019 em Wuhan, China, desencadeou uma crise emergencial em saúde global. Em resposta, vacinas foram desenvolvidas rapidamente para conter a propagação da doença e mitigar casos graves. No Brasil, diversas plataformas de vacinas foram empregadas, incluindo aquelas baseadas em mRNA (BNT162), vetor de adenovírus (ChAdOx1) e vírus inativado (CoronaVac). Grupos com comorbidades e doenças crônicas foram considerados prioritários para receberem as vacinas, destacando a importância de avaliar a resposta imune pós-vacinação em indivíduos com alergias respiratórias, dada a via de entrada do SARS-CoV-2 pelas vias respiratórias. Avaliar o impacto do nível de atividade física na resposta imune vacinal também pode fornecer informações importantes sobre os mecanismos imunológicos subjacentes à proteção conferida pela vacinação. Este estudo é composto de três capítulos, onde, no primeiro, investigamos os efeitos adversos pós-vacinação contra SARS-CoV-2 em indivíduos com diagnóstico de atopia e controles saudáveis. Observamos que os indivíduos atópicos vacinados com ChAdOx1 apresentaram maior incidência de efeitos adversos em comparação aos não atópicos, embora nenhum participante tenha relatado reações alérgicas graves ou anafilaxia; no segundo capítulo, investigamos o desempenho de uma plataforma de teste *point-of-care* (POC), que se baseia no teste rápido de imunocromatografia de fluxo lateral. Esta plataforma se revelou uma importante ferramenta na determinação da prevalência de anticorpos neutralizantes (NAbs) em indivíduos vacinados. Observamos que os indivíduos vacinados apresentaram níveis mais elevados de anticorpos em comparação aos convalescentes e àqueles sem infecção prévia (*naïve*), destacando a utilidade dessa plataforma no monitoramento da infecção, permitindo o rastreamento preciso de grupos de risco e a avaliação da eficácia das vacinas. No terceiro capítulo, investigamos a resposta imune humoral pós-vacinação para COVID-19 entre homens e mulheres em relação ao seu nível de atividade física, por meio da avaliação quantitativa de adipocinas pró e anti-inflamatórias. Independentemente do seu *status* de sedentarismo ou atividade, as mulheres apresentaram uma tendência maior de efetividade à vacina, evidenciada por níveis elevados de anticorpos IgG anti-S (*Spike*), em comparação aos homens, apesar da presença aumentada de adipocinas inflamatórias, como a leptina e resistina. Os níveis dessas adipocinas podem desempenhar um importante papel na eficácia vacinal, embora outros fatores biológicos devam ser melhor avaliados, como genéticos e hormonais. Em conclusão, os padrões de resposta imune identificados neste estudo indicam que o nível de atividade física pode influenciar de maneira distinta a resposta vacinal, especialmente em mulheres, denotando a

necessidade de levar em consideração diferentes perfis na elaboração de políticas públicas que orientam as estratégias de vacinação em uma população específica. No quarto capítulo, investigamos a relação entre atopia, adipocinas e o impacto da atividade física, avaliando a atopia por meio de níveis de IgE e teste cutâneo de puntura para aeroalérgenos, quantificação de adipocinas séricas, como leptina, resistina e adiponectina. Observamos que indivíduos atópicos independentemente do nível de atividade física apresentam menor produção de leptina em comparação aos não atópicos, e que esse comportamento continua quando adicionamos a variável atividade física, sendo os atópicos sedentários apresentando maiores níveis de resistina e menores níveis de leptina comparado aos não atópicos. Por outro lado, os indivíduos atópicos que praticam atividade física possuem aumento dos níveis de adiponectina, anti-inflamatória, comparado aos de comportamento sedentário. O índice de massa corpórea pode influenciar a produção dessas adipocinas, em indivíduos atópicos e obesos que apresentaram maiores níveis de leptina comparado aos não-obesos. Com esse estudo, concluímos que o exercício físico é capaz de modular as respostas imunológicas em indivíduos atópicos podendo alterar os sintomas da rinite alérgica.

Palavras-chave: COVID-19, vacinação, atopia, alergia respiratória, exercício físico, adipocinas

ABSTRACT

COVID-19, caused by SARS-CoV-2 and initially identified in 2019 in Wuhan, China, triggered an emergency global health crisis. In response to this status, vaccines were quickly developed to contain the spread of the disease and mitigate severe cases. In Brazil, most of these vaccine platforms have been used, including those based on mRNA (BNT162), adenovirus vector (ChAdOx1), and inactivated virus (CoronaVac). Groups with comorbidities and chronic diseases were considered a priority to receive the vaccines, highlighting the importance of evaluating the post-vaccination immune response in individuals with respiratory allergies, given the route of entry of SARS-CoV-2 through the respiratory tract. Assessing the impact of physical activity level on the vaccine immune response can also provide important information about the immunological mechanisms underlying the protection conferred by vaccination. This study has been presented in three chapters. First, we investigated the adverse effects post-vaccination against SARS-CoV-2 in individuals with atopy and healthy controls. We observed that atopic individuals vaccinated with ChAdOx1 had a higher incidence of adverse effects compared to non-atopic individuals, although no participants reported severe allergic reactions or anaphylaxis. In the second chapter, we investigate the performance of a point-of-care (POC) testing platform, which is based on the rapid lateral flow immunochromatography test. This platform proved to be an important tool in determining the prevalence of neutralizing antibodies (NAbs) in vaccinated individuals. We observed that vaccinated individuals had higher levels of antibodies compared to convalescents and those without previous infection (naïve), highlighting the usefulness of this platform in monitoring infection, accurate tracking of risk groups, and assessment of vaccine effectiveness. In the third chapter, we investigated the humoral immune response post-vaccination for COVID-19 among men and women in relation to their level of physical activity, through the quantitative evaluation of pro and anti-inflammatory adipokines. Regardless of their status of sedentary lifestyle or activity, women showed a greater tendency of vaccine effectiveness, evidenced by elevated levels of anti-S IgG antibodies (Spike), compared to men, despite the increased presence of inflammatory adipokines, like leptin and resistin. The levels of these adipokines may play an important role in vaccine efficacy although other biological features must be investigated, such as genetic and hormonal factors. In conclusion, the immune response patterns identified in this study indicate that allergy/atopy status can influence the vaccine response with several aspects, especially in women, denoting the need to take different profiles into account when developing public policies that guide strategies of vaccination in a specific population. In the fourth chapter, we

investigated the relationship between atopy, adipokines and the impact of physical activity, assessed atopy through IgE levels and skin prick test for aeroallergens, quantification of serum adipokines, such as leptin, resistin and adiponectin. We observed that atopic individuals regardless of the level of physical activity have lower leptin production compared to non-atopic individuals, and that this behavior continues when we add the variable physical activity, with higher levels of resistin and lower levels of leptin compared to non-atopic. On the other hand, atopic individuals who practice physical activity have increased levels of adiponectin, anti-inflammatory, compared to sedentary behavior. The body mass index can influence the production of these adipokines in atopic and obese individuals who had higher levels of leptin compared to non-obese individuals. With this study, we conclude that physical exercise is capable of modulating immune responses in atopic individuals and may alter the symptoms of allergic rhinitis.

Keywords: COVID-19, vaccination, atopy, respiratory allergy, physical exercise, adipokines.

LISTA DE ABREVIATURAS

ACE2: Enzima conversora de angiotensina 2

APC: Célula apresentadora de Antígeno

ADCC: Citotoxicidade mediada por células dependente de anticorpos

ADCP: Fagocitose celular dependente de anticorpos

ANVISA: Agência Nacional de Vigilância Sanitária

BNT162: Vacina da Pfizer-BioNTech

BNT612b2: Vacina da Pfizer-BioNTech

B.1.17: Variante Alfa

B.1.351: Variante Beta

BA.4: Subvariante da variante Ômicron

BA.5: Subvariante da variante Ômicron

CD40L: Ligante de molécula CD40

CDC: Citotoxicidade dependente de complemento

ChAdOx1: *Chimpanzee Adenovirus Oxford 1* - Vacina Covishield/Vaxzevria (AstraZeneca)

COVID-19: Doença infecciosa por coronavírus 2019

Der f 1: Alérgeno do grupo 1 de *Dermatophagoides farinae*

Der p 1: Alérgeno do grupo 1 de *Dermatophagoides pteronyssinus*

Fab: Fragmento de ligação ao antígeno

Fc: Fragmento cristalizável

Fcε: Receptor da imunoglobulina E (IgE)

FcεRI: Receptor de alta afinidade da imunoglobulina E (IgE)

FDA: Administração de alimentos e medicamentos (*Food and Drug Administration*)

HDM: Ácaros da poeira domiciliar (*House Dust mite*)

HIV: Vírus da imunodeficiência humana

IFN-γ: Interferon gama

IgA: Imunoglobulina A

IgE: Imunoglobulina E

IgG: Imunoglobulina G

IgG1: Subclasse 1 da Imunoglobulina G

IgG4: Subclasse 4 da Imunoglobulina G

IgM: Imunoglobulina M

IL-2: Interleucina 2

IL-5: Interleucina 5
IL-4: Interleucina 4
IL-6: Interleucina 6
IL-9: Interleucina 9
IL-10: Interleucina 10
IL-13: Interleucina 13
IL-17: Interleucina 17
IL-22: Interleucina 22
IL-25: Interleucina 25
IL-33: Interleucina 33
ILC2: Células linfoides inatas do Tipo 2
IPAQ: Questionário Internacional de Atividade Física
JNK: Proteína cinase do Tipo *Janus*
JN.1: Subvariante JN.1 da variante Ômicron
LPA: Lesão pulmonar aguda
M2: Macrófagos do Tipo 2
MERS-CoV: Síndrome Respiratória do Oriente Médio-Coronavírus
MHC: Complexo de histocompatibilidade
MHC I: Complexo de histocompatibilidade do Tipo I
MHC II: Complexo de histocompatibilidade do Tipo II
mRNA: Ácido ribonucleico do Tipo mensageiro
mRNA-1273: Vacina Spikevax (Moderna)
N: Nucleocapsídeo
NAbs: Anticorpos neutralizantes
NF-κB: Fator de transcrição nuclear kappa B
NTD: Domínio N-terminal da proteína S1
OMS: Organização Mundial da Saúde
P38MAPK: Proteína quinase ativada por mitógeno
PAR: Rinite alérgica perene
PNI: Programa Nacional de Imunizações
PPPs: Parcerias público-privada
P.1: Variante Gamma
RA: Rinite alérgica
RBD: Domínio de ligação ao receptor

RNA: Ácido ribonucleico

ROS: Espécie reativa de oxigênio

S: espícula (*spike*)

S1: Subunidade 1 (superior) da proteína *spike*

S2: Subunidade 2 (inferior) da proteína *spike*

SAR: Rinite alérgica sazonal

SARS-CoV-2: Coronavírus 2 da Síndrome Respiratória Aguda Grave

SRAA: Renina angiotensina aldosterona

ssRNA: RNA fita-simples de sentido negativo

SIH-SUS: Sistema de Informações Hospitalares do Sistema Único de Saúde

SUS: Sistema Único de Saúde

T CD4⁺: Célula T auxiliar que expressa o marcador CD4

T CD8⁺: Célula T citotóxica que expressa o marcador CD8

TCP: Teste Cutâneo de Puntura

Th1: Célula T auxiliar Tipo 1

Th2: Célula T auxiliar Tipo 2

Th9: Célula T auxiliar Tipo 9

Th17: Célula T auxiliar Tipo 17

Th22: Célula T auxiliar Tipo 22

TLR: Receptor Tipo *Toll*

TNF: Fator de necrose tumoral

TNF- α : Fator de necrose tumoral do Tipo alfa

TMPRSS2: Serina protease transmembrana Tipo 2

Treg: Células T reguladora

TSLP: Linfopoietina estromal tímica

VOC: Variante de preocupação

VOI: Variante de interesse

Sumário

1. FUNDAMENTAÇÃO TEÓRICA	15
1.1 COVID-19	16
1.2 SARS-CoV-2 e resposta imune na COVID-19	17
1.3 Variantes de preocupação (VOC).....	21
1.4 Vacinas para COVID-19	22
1.5 Doenças alérgicas respiratórias	26
1.6 Aeroalérgenos.....	28
1.7 Asma.....	29
1.8 Rinite Alérgica.....	32
1.9 Alergias respiratórias e COVID-19	33
1.10 Exercício físico e COVID-19	35
1.11 O papel das adipocinas no exercício físico.....	37
2. OBJETIVOS.....	39
2.1 Objetivo geral	39
2.2 Objetivos específicos.....	39
REFERÊNCIAS BIBLIOGRÁFICAS	40
3. ATOPIA E PERFIL DE SEGURANÇA DAS VACINAS DE COVID-19.....	58
3.1 Manuscrito publicado	59
2. CORRELATO DE IMUNIDADE INDUZIDOS POR VACINAS ESPECÍFICAS E SUA EFICÁCIA NA PROTEÇÃO CONTRA COVID-19	71
2.1. Carta de apresentação: <i>Expert Review of Molecular Diagnostics</i>	72
2.2. Manuscrito	74
3. O PAPEL DA ATIVIDADE FÍSICA NA RESPOSTA IMUNE ÀS VACINAS CONTRA COVID-19	94
3.1 Carta de apresentação: <i>Journal of Sports Medicine</i>	95
3.1. Manuscrito	97

4. EXERCÍCIOS FÍSICOS NA ALERGIA RESPIRATÓRIA.....	130
4.1. Carta de apresentação: <i>Expert Review of Respiratory Medicine</i>	131
4.2. Manuscrito	133
5. CONSIDERAÇÕES FINAIS	157
5.1. Contribuições para a saúde pública	158
5.2. Conclusões finais.....	159
ANEXO 1	0
ANEXO 2	2
ANEXO 3	3
ANEXO 4	4
ANEXO 5	8

APRESENTAÇÃO

A estrutura apresentada neste documento segue um padrão recomendado pelo Programa de Pós-graduação em Imunologia e Parasitologia Aplicadas da Universidade Federal de Uberlândia (PPGIPA/UFU).

O formato desta tese inclui uma fundamentação teórica, com base nos temas propostos no estudo, bem como os objetivos avaliados. Além disso, o documento inclui ainda três manuscritos, sendo um deles já publicado e outros que ainda estão em processo de submissão. Os manuscritos estão divididos em capítulos, de acordo com as seguintes linhas temáticas:

- I) Atopia e perfil de segurança das vacinas de COVID-19
- II) Correlatos de imunidade induzidos por vacinas específicas e sua eficácia na proteção contra COVID-19
- III) O papel da atividade física na resposta imune às vacinas contra COVID-19
- IV) Exercícios físicos na alergia respiratória

Por fim, o documento apresenta as principais considerações finais, contendo a síntese das principais conclusões do estudo, com base na análise de cada um dos capítulos.

1. Fundamentação teórica

1.1 COVID-19

A COVID-19, uma doença que foi reportada pela primeira vez na cidade de Wuhan, província de Hubei, China, é responsável por desencadear nos pacientes pneumonia grave e, meses após o primeiro caso, foi declarada uma Emergência de Saúde Pública Internacional pela Organização Mundial da Saúde (OMS) (Worobey *et al.*, 2022). O agente etiológico da doença é o SARS-CoV-2 (Coronavírus de Tipo 2 da Síndrome Respiratória Aguda Grave), causador da Síndrome Respiratória Aguda Grave, responsável por disseminá-la para o mundo todo com alto nível de transmissão e potencial pandêmico e considerável influência no estilo de vida e mundo que vivemos (Hao *et al.*, 2022).

No ano de 2020 a 2021, durante o estado de emergência, mais de 14,9 milhões de mortes foram notificadas, com os Estados Unidos, Índia e Brasil liderando os maiores números de casos confirmados. No Brasil, os casos confirmados e o número de mortos em 2020 foram de 1,5 milhões, com 2,8% de letalidade, sendo o segundo país a registrar o maior número de mortos no mundo (Siddiqui *et al.*, 2021; Nucci *et al.*, 2023). De fato, o elevado número de casos diários graves, que resultavam em internações, sobrecarregou os sistemas públicos e privados de saúde, incluindo o Sistema Único de Saúde (SUS), principalmente por ocupar a maioria dos leitos dos hospitais municipais, estaduais, federais e privados, além de trazer à tona a falta de equipamentos de proteção individual e instrumentos para profissionais de saúde (Palamim; Marson, 2020). Além disso, a drástica mudança de comportamento necessária para controlar a progressão do vírus em todo o mundo, potencializou diversos problemas econômicos, sociais e psicossociais em muitos países, principalmente o fechamento de empresas e transição do regime de trabalho presencial para o *home-office*, caracterizado pela condução do trabalho em ambiente residencial (Mendonça *et al.*, 2022). Seguindo as recomendações da OMS, medidas de isolamento social, como a quarentena, foram implementadas pelos representantes dos diversos países do mundo, onde fronteiras e cidades foram fechadas, sendo mantidos apenas serviços essenciais, seguidos de recomendações quanto ao uso de máscaras de proteção contra aerossóis e proibição de aglomeração populacional em locais públicos (Silva *et al.*, 2020; Seddighi; Dollard; Salmani, 2022) (Seddighi *et al.*, 2022; Silva *et al.*, 2020).

A partir dessas ações, a quebra financeira das pequenas empresas e o aumento do desemprego tornaram-se inevitáveis no Brasil, seguidos da queda dos indicadores econômicos e aumento da inflação e, conseqüentemente, dos preços dos produtos, levando a graves problemas sociais e econômicos, como pobreza, fome, aumento da desigualdade social e perda de qualidade de vida, com reflexos em outros indicadores, como na educação (Carvalho; Viola; Sperandio, 2021; Mckibbin; Fernando, 2023). Conseqüentemente, problemas psicossociais,

como depressão, estresse e ansiedade, aumentaram durante a pandemia, principalmente entre profissionais de saúde, mulheres, desempregados, idosos e jovens, devido ao estresse, medo e incerteza sobre o tratamento e a progressão da doença, medidas de confinamento e instabilidade socioeconômica (Pfefferbaum; North, 2020; Naseer *et al.*, 2023).

1.2 SARS-CoV-2 e resposta imune na COVID-19

O SARS-CoV-2 está incluído na família Coronaviridae que se divide em duas subfamílias Letovirinae e Orthocoronavirinae, nesta última divide-se em quatro gêneros Alphacoronavirus, Betacoronavírus, Gammacoronavírus e Deltacoronavírus (Zmasek *et al.*, 2022). O gênero Betacoronavirus possui associação com doenças respiratórias humanas de grande importância como Coronavírus da Síndrome Respiratória Aguda Grave (SARS-CoV) e Coronavírus da Síndrome Respiratória do Oriente Médio (MERS-CoV) (Cui; Li; Shi, 2019; Verma; Subbarao, 2021). Como outros membros da família Coronaviridae, o genoma SARS-CoV-2 é composto por uma única fita de RNA de senso positivo (+ ssRNA) com aproximadamente 29,9kb, adicionado a quatro proteínas estruturais: nucleocapsídeo (N), membrana (M), espícula (S) e envelope (E) (Naqvi *et al.*, 2020).

A transmissão do SARS-CoV-2 geralmente ocorre de pessoa para pessoa, por gotículas expelidas durante a fala, tosse ou espirro, com possibilidade de transmissão de indivíduos assintomáticos (Schijven *et al.*, 2021; Leo *et al.*, 2023). No entanto, a contaminação por contato em superfícies também foi descrita. O período de incubação é de 5 dias, em média (Lauer *et al.*, 2020), com sintomas bem definidos, como febre, tosse e dispneia, embora, em alguns casos, a doença possa evoluir para a forma grave, muitas vezes necessitando de respiração mecânica (Hu; Huang; Yin, 2021). Idosos e indivíduos com comorbidades graves (obesidade, doenças cardiovasculares, hipertensão, diabetes e doença pulmonar obstrutiva crônica) são mais suscetíveis à hospitalização (Garg *et al.*, 2020).

A infecção por SARS-CoV-2 se inicia no trato respiratório superior pela interação entre a glicoproteína S viral e a enzima conversora de angiotensina 2 do hospedeiro (ACE2), além da serina protease transmembrana tipo 2 (TMPRSS2), que permite a entrada do vírus na célula hospedeira (Zhu; Sharma; Chang, 2023). Embora os pulmões sejam a primeira linha de contato do vírus, geralmente os tecidos extrapulmonares, como dermatológicos, neurológicos, oftalmológicos, endocrinológicos, hepatobiliares, gastrointestinais, renais, cardiovasculares e/ou hematológicos podem ser afetados (Gupta *et al.*, 2020; Grune *et al.*, 2024). A fisiopatologia e o dano tecidual estão relacionados com o aumento da carga viral que tem como consequência

danos às células endoteliais, inflamação trombótica, desregulação da resposta imune e desregulação do sistema renina-angiotensina-aldosterona (SRAA) (Mascolo *et al.*, 2021).

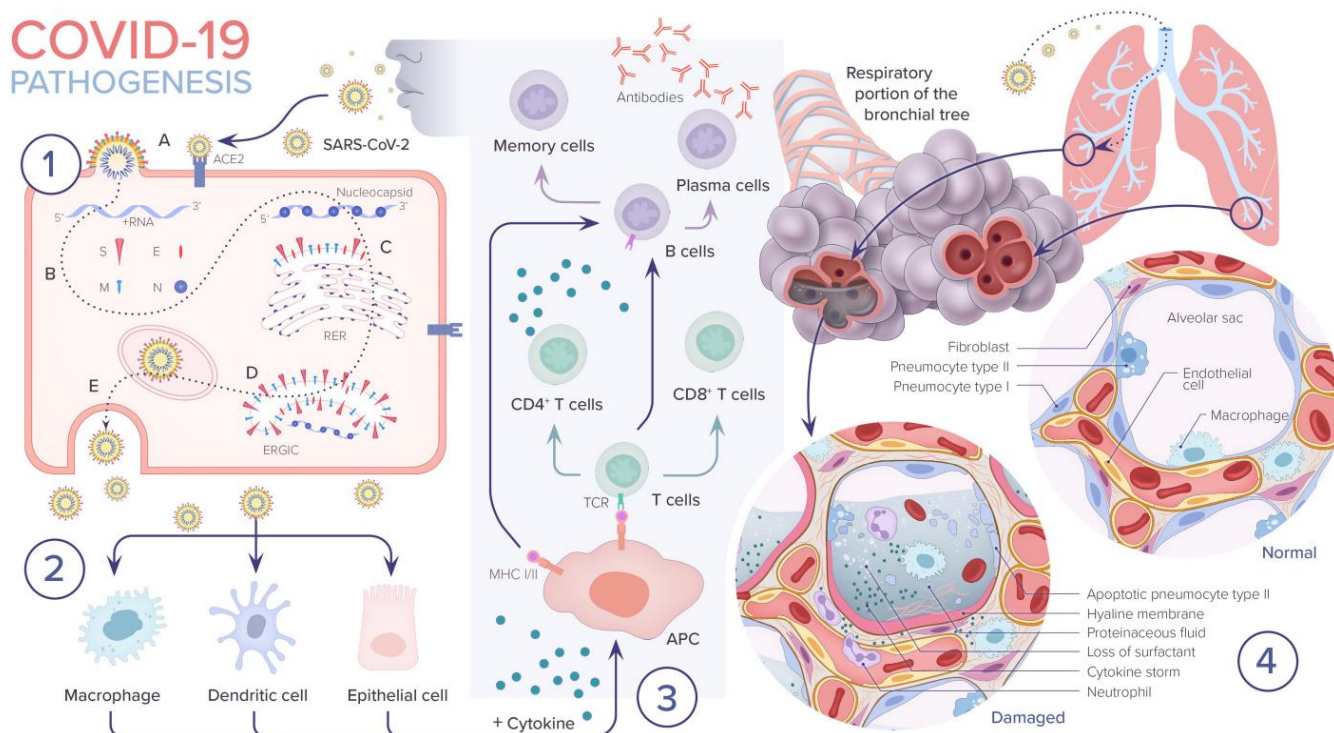


Figura 1. Representação da patogênese da COVID-19. **1.** O SARS-CoV-2 entra na célula hospedeira através do receptor ACE2 presente nas células das vias respiratórias superiores, liberando o RNA viral no citoplasma. **2.** A infecção e multiplicação do SARS-CoV-2 desencadeiam uma resposta inflamatória mediada pela ativação de macrófagos e células dendríticas. **3.** O vírus é apresentado pelas células apresentadoras de antígeno (APCs) via Complexo Principal de Histocompatibilidade I e II (MHC I e MHC II), estimulando tanto a imunidade humoral quanto a celular, resultando na produção de anticorpos e citocinas, respectivamente. **4.** Em casos graves de COVID-19, o vírus infecta células pulmonares onde se multiplicam, induzindo a apoptose, o que resulta em perda da capacidade respiratória. Isso é exacerbado pelo influxo de macrófagos e neutrófilos. Juntos, esses componentes induzem a liberação de uma grande quantidade de citocinas pró-inflamatórias, processo conhecido como “tempestade de citocinas”. *Fonte: Chams et al., 2020.*

A patogênese da doença ocorre quando o vírus SARS-CoV-2 entra na célula hospedeira, provocando uma ativação exacerbada do sistema imune, um evento reconhecido como “tempestade de citocinas”. Isso ocorre, pois, as células T CD4⁺, também conhecidas como T *helper*, são ativadas, liberando várias citocinas de forma abruptamente exagerada, como visto em outras infecções virais, como dengue e influenza. Entretanto, somente alguns pacientes desenvolvem essa síndrome inflamatória aguda, algumas pesquisas tem relatado a existência de indivíduos com polimorfismos genéticos nos receptores do tipo *Toll-like* (TLR), responsáveis pela ligação do antígeno, cujas alterações afetam diretamente as respostas do

indivíduo a certas infecções (Alhabibi, *et al.*, 2023). Uma das manifestações clínicas causadas por essa ativação extrema do sistema imune com citocinas inflamatórias é a lesão pulmonar aguda (LPA), que é grave em pacientes com COVID-19 e que pode levar o indivíduo a óbito, em situação semelhante à observada em pacientes infectados com SARS-CoV e MERS-CoV. Os relatos mostraram que os primeiros pacientes que foram infectados com SARS-CoV-2 na cidade de Wuhan apresentaram o quadro de LPA com alta concentração de citocinas pró-inflamatórias e quimiocinas no plasma, levando a necessidade de tratamento hospitalar de cuidado intensivo em função da forma grave da doença, o que não ocorreu em indivíduos doentes moderados e leves. Situação semelhante foi evidenciada em todo o curso da pandemia de COVID-19, o que conota o padrão de evolução clínica dos pacientes infectados pelo vírus (Chams *et al.*, 2020; Borczuk; Yantiss, 2022).

A citocina IL-6 exerce um dos principais papéis na inflamação induzida por SARS-CoV-2, devido à atuação fundamental na “tempestade de citocinas” e durante o curso da infecção. No processo da entrada do vírus, é responsável por se ligar nos receptores solúveis e transmembranares das células, provocando a ativação inflamatória do sistema imune, potencializando a liberação exacerbada das demais citocinas e quimiocinas (Zhang *et al.*, 2020a; Chen; Quach, 2021). Essa citocina também é um fator da janela de oportunidade na busca de tratamentos para amenizar sintomas graves da COVID-19, como o desenvolvimento de anticorpos monoclonais anti-IL-6 como o Tocilizumab que é capaz de inibir a produção de IL-6 contribuindo para amenização dos sintomas impedindo o avanço dos pacientes para óbito, além disso se mostrou eficaz em disfunções inflamatórias crônicas e agudas que tem como alvo a patogênese da doença.

A produção de anticorpos IgM, IgA e IgG produzidos pelo sistema imune contra as proteínas virais S e N apresentam importante papel no controle da infecção pelo SARS-CoV-2, sendo detectados em diferentes períodos pós-infecção. A resposta de anticorpos específicos à região RBD bem como outras regiões da proteína S são variadas, dependendo da gravidade da doença. Alguns estudos demonstraram que essa resposta é reduzida após 6 meses da infecção, e isso torna o indivíduo suscetível a novas infecções após esse período (Dinç *et al.*, 2022). As diferentes classes de anticorpos desempenham funções distintas, mas o seu sinergismo resulta na neutralização do vírus (Murin; Wilson; Ward, 2019). Por exemplo, a IgM é detectável apenas na fase inicial da infecção, mas em casos graves sua presença é observada até 21 dias. Por outro lado, a IgA sérica tem função de agravar os sintomas após a infecção aguda, entretanto, a IgA secretora na saliva pode ser detectada entre 49 a 73 dias após os sintomas, possuindo uma função protetora ou neutralizadora capaz de responder rapidamente e

eficazmente as infecções virais (Cervia *et al.*, 2021). A produção de IgG com papel neutralizante é observada em casos de indivíduos com infecção grave em comparação aos casos leves, todavia, nesse sentido, a distribuição e a dinâmica dos anticorpos devem estar associadas à particularidade de cada indivíduo, principalmente considerando as comorbidades, carga viral e outros fatores que influenciam na gravidade da doença (Pang *et al.*, 2021; Assaid *et al.*, 2023).

Os anticorpos neutralizantes (NAbs) são cruciais para proteção contra o vírus, sua função de base inclui a diminuição da carga viral, bloqueando a entrada nas células hospedeiras por meio da ligação às proteínas do envelope viral, promovendo sua alteração conformacional e tornando-as não-funcionais, o que impede a fusão entre o vírus e a membrana da célula e a consequente entrada para replicação. Esses diferentes mecanismos de bloqueio dos NAbs possibilitam determinar a amplitude e a potência da capacidade de neutralização do vírus (Tam *et al.*, 2024).

Para compreensão dos diferentes mecanismos de bloqueio, é importante diferenciar vírus envelopados de classe I e II. Naqueles de classe I, a entrada do vírus ocorre na ligação entre a superfície das células hospedeira em receptores específicos, onde uma única proteína do envelope é responsável pela fusão, ao contrário dos vírus de classe II, que precisam ser internalizados por endocitose, necessitando de proteínas de pré-fusão que sofrem alterações conformacionais, expondo a estrutura de fusão da membrana. O SARS-CoV-2, portanto, é considerado vírus envelopado de classe I, que utiliza como mecanismo de bloqueio o receptor do hospedeiro, onde a proteína do envelope do vírus interage com receptor da célula de interesse, iniciando a primeira etapa da infecção (Tam *et al.*, 2024). Os NAbs, entretanto, possuem interações que são abrangentes em relação ao vírus da COVID-19, devido a capacidade de ligação com outros receptores ACE2, localizados na maioria das células do hospedeiro, assim há evidências que os níveis de NAbs possuem correlação proporcional à manutenção da doença. Por outro lado, a ausência de resposta de anticorpos neutralizantes é preditiva de mortalidade e aumento do controle viral (Dispinseri *et al.*, 2021; Abebe; Dejenie, 2023).

Os NAbs específicos para SARS-CoV-2 são produzidos por meio da infecção natural ou estratégias de vacinação pelo organismo. As funções efetoras são observadas por meio da ligação através das porções Fab do anticorpo, que é capaz de neutralizar e promover a redução da carga viral, a porção Fc é a que promove inibição do avanço da infecção viral pela citotoxicidade mediada por células dependente de anticorpos (ADCC), fagocitose celular

dependente de anticorpos (ADCP) e citotoxicidade dependente de complemento (CDC) (Li *et al.*, 2022a; Li; Chang, 2023).

Estudos tem relatado que indivíduos convalescentes, ou seja, recuperados da infecção contra SARS-CoV-2, apresentaram baixos níveis de NAbs, em comparação aos pacientes hospitalizados. Uma vez que os NAbs apresentam funções bem definidas, a proporção destes anticorpos também precisa ser considerada, pois há relatos de diferenças nas titulações de NAbs durante a infecção, sendo assim, não considerado como principal marcador de correlato de proteção (Seow *et al.*, 2020; Pang *et al.*, 2021).

Nas últimas décadas, NAbs com grande potencial neutralizador estão sendo utilizados em terapias antivirais com eficácia admirável, como os NAbs anti-SARS-CoV-2, como Sotrovimab, Bebtelovimab e REGEN-COV2, que demonstraram possuir uma alta prevenção de sintomas graves e redução de hospitalização durante a crise pandêmica (Gupta *et al.*, 2022; Hentzien *et al.*, 2022). Uma grande vantagem destes anticorpos é que possuem alta especificidade e sua estrutura pode ser alterada para efeitos terapêuticos específicos minimizando a imunogenicidade por meio de técnicas de engenharia molecular, além de ser uma estratégia promissora para minimizar infecções de novas variantes. No entanto, as desvantagens incluem: altos custos de produção, curto prazo de validade e falta de pessoal especializado para manuseio, o que ocasionam limitações particulares na aplicabilidade desses anticorpos (Tam *et al.*, 2024).

A técnica utilizando NAbs contra a infecção do SARS-CoV-2 geralmente é direcionada para alvos estratégicos do vírus, a proteína RBD e domínio NTD das subunidades S1 e S2. Os anticorpos são classificados de acordo com a região de ligação aos epítomos. Os de classe 1 reconhecem a região superior da molécula RBD e a classe 2 a região inferior, já os anticorpos de classe 3 reconhecem vários sítios de ligação da molécula ACE2 e podem se ligar independente da região à proteína RBD. Os de classe 4 são capazes de se ligarem a regiões altamente conservadas do domínio RBD (Wang; Wang; Zhou, 2023). O avanço dessas tecnologias utilizando esses NAbs específicos para diversos alvos de proteínas virais podem contribuir na redução de casos e minimizar o avanço das infecções por diferentes tipos de variantes de SARS-CoV-2.

1.3 Variantes de preocupação (VOC)

A cepa selvagem de Wuhan, inicialmente gerou a doença COVID-19, através dela diversas novas variantes foram detectadas ao longo da pandemia e foram classificadas como variante de interesse (VOI) e variantes de preocupação (VOC). As variantes VOI são de

interesse devido ao seu alto índice de mortalidade, escape imunológico, prevalência mundial com aumento desenfreado de casos ao longo do tempo, desencadeadora de impactos epidemiológicos e dentre outros que afetam a saúde pública global. As variantes de preocupação (VOC) possuem características semelhantes à anterior, entretanto está associada a graus de significância em relação ao aumento da transmissibilidade, aumento da virulência ou alterações clínicas da doença, diminuição da eficácia de medidas sociais, diagnósticos e vacinas disponíveis. As VOCs são variantes de SARS-CoV-2 que resultam de mutações genéticas que afetam a interação entre a proteína S e seu receptor ACE2 nas células hospedeiras. Essas alterações trazem reflexos na resposta imune, na gravidade da doença e na transmissibilidade do vírus (Choi; Smith, 2021; Aleem; Akbar Samad; Vaqar, 2024).

Diversas variantes surgiram ao longo do tempo como a Alfa (B.1.1.7) identificada no Reino Unido, Beta (B.1.351), inicialmente identificada na África do Sul, e Gamma (P.1), de origem no Brasil, entretanto a Ômicron é a variante atualmente dominante no mundo e que, apesar de exibir elevado potencial de transmissão e apresenta em comum às demais cepas a presença de mutações pontuais na proteína S do vírus, especialmente na região do domínio de ligação ao receptor (RBD) (Ren *et al.*, 2022). Ao final de 2022, foram identificadas em 36 países duas importantes subvariantes da Ômicron, denominadas BA.4 e BA.5, que se diferem das demais por apresentarem mutações no resíduo L452 e FA86V do receptor do domínio de ligação (RBD) da proteína S (Hachmann *et al.*, 2022; Setiabudi *et al.*, 2022). Em 2023, a subvariante da Omicron BA.2 foi identificada como JN.1 (BA.2.86), apresentando três mutações na proteína S, que resulta na maior transmissão e capacidade de escape imunológico em relação ao vírus ancestral (Wuhan). Entretanto, não há evidências que demonstram a ocorrência de sintomas graves, mas apenas moderados e leves (Kamble *et al.*, 2024).

As VOCs, além de aumentarem o potencial de transmissão, apresentam capacidade de reinfeção em indivíduos que recuperaram de infecções subjacentes, acompanhado de diminuição de anticorpos no soro (Choi; Smith, 2021). Além disso, há uma preocupação premente quanto à situação vacinal a nível mundial, apesar da eficácia das vacinas atualmente disponíveis, deve-se reforçar a necessidade de monitoramento dessas variantes para avaliação de impactos no controle do vírus bem como futuros impactos.

1.4 Vacinas para COVID-19

As vacinas possuem uma complexa interação entre o sistema imune do hospedeiro e os antígenos específicos que são capazes de desencadear respostas imunes. Estas substâncias antigênicas encontradas nas fórmulas vacinais, frequentemente são fragmentos de

microrganismos patogênicos ou seus produtos derivados, que são reconhecidas pelas células apresentadoras de antígenos (APC), tais como macrófagos e células dendríticas, que os processam e apresentam aos linfócitos T *helper*. Em resposta, estas células são ativadas, secretando citocinas e expressando moléculas co-estimulatórias, sinais indispensáveis para o recrutamento e ativação de linfócitos B. Estes, por sua vez, diferenciam-se em plasmócitos, gerando uma resposta humoral caracterizada pela produção de anticorpos específicos contra os antígenos vacinais. Esses anticorpos, em cooperação com outras células do sistema imune, conferem proteção ao organismo hospedeiro contra futuros contatos com os alvos patogênicos, resultando na ativação da imunidade adquirida e a prevenção de doenças infecciosas (Li *et al.*, 2022b; Zhao *et al.*, 2024).

O desenvolvimento de vacinas durante a pandemia de COVID-19 se tornou a melhor opção para o controle da incidência da infecção e mortalidade no mundo todo. Pesquisadores, aliados às estratégias colaborativas de empresas farmacêuticas, uniram esforços para desenvolvimento de novas tecnologias, em associação às demais pré-existentes, visando agilidade e urgência para aplicação na população, com a meta de controle da pandemia pelo SARS-CoV-2 (Patel *et al.*, 2022). Grande parte destas tecnologias foram aprovadas no Brasil e passaram a integrar o portfólio vacinal do Programa Nacional de Imunizações (PNI), incluindo vacinas baseadas em vírus inativado, mRNA e vetor de adenovírus.

As vacinas de vírus inativado contêm cepas replicantes que passaram por um processo físico e químico que são incapazes de causar doença, e são relevantes em relação das que possuem componentes ou patógenos inteiros mortos. Uma objeção encontrada em sua administração é a restrição aos indivíduos com imunodeficiências primárias ou infectados com HIV, e com uso de medicamentos imunossupressores, que podem ter riscos de replicação do patógeno de forma descontrolada (Pollard; Bijker, 2021). Um exemplo de vacina que utiliza essa tecnologia é a CoronaVac desenvolvida pela empresa chinesa Sinovac Biotech. Nesta, o esquema vacinal consiste em duas doses com intervalo de 15 dias (Jin *et al.*, 2022).

Em estudos clínicos de fase I e II da CoronaVaC, realizados em adultos, crianças e adolescentes, foram relatados em 20% dos participantes efeitos adversos leve a moderado após primeira dose, sendo a dor local o efeito mais relatado. Todos tiveram soroconversão após segunda dose (Han *et al.*, 2021; Wu *et al.*, 2021). Em reinfecções de COVID-19 participantes sintomáticos do estudo de fase III apresentaram após a vacinação uma eficácia de 83,5% com a segunda dose. Os efeitos adversos sistêmicos e locais mais relatados foram fadiga e dor local, respectivamente (Tanriover *et al.*, 2021).

As vacinas baseadas em vetor de adenovírus, como a ChAdOX1, da fabricante AstraZeneca, utilizam uma tecnologia baseada em adenovírus de chimpanzé que codifica a glicoproteína antigênica S como veículo para entregar o material genético de um patógeno alvo ao organismo hospedeiro. Esses vetores adenovirais são projetados para serem seguros e incapazes de causar doença, mas ainda capazes de induzir uma resposta altamente imunogênica ativando respostas imunes inatas e adaptativas (Elkashif *et al.*, 2021; Spencer *et al.*, 2022). Os estudos de fase I e II da ChAdOx1 demonstraram que, após a vacinação, indivíduos relataram efeitos adversos locais e sistêmicos leve a moderados, e uma pequena porcentagem relatos de gravidade. O aumento no título de anticorpos IgG anti-S foi observado 28 dias após a segunda dose da vacina, que se manteve até 12 meses. Outros estudos de imunogenicidade e segurança, cuja resposta foi avaliada em indivíduos em até 6 meses da aplicação, demonstraram aumento nos títulos de NAbs no 57º dia, com diminuição a partir do 180º dia. A respeito de reinfecções, não houve casos graves da COVID-19 em nenhum grupo vacinado (Hamaluba *et al.*, 2023; Kulkarni *et al.*, 2024). Nos estudos de fase IV indivíduos soronegativos que tomaram a ChAdOx1 78-80% relataram efeitos adversos leves e moderados e 1-8% alertaram possuir efeitos graves após vacinação, o aumento de NAbs foi observado no dia 29 e após a dose de reforço (Voysey *et al.*, 2021; Ramasamy *et al.*, 2023). Além disso, outra vacina que utiliza o mesmo mecanismo é a Ad26.COV2 (Janssen), que em estudos clínicos demonstrou eficácia de aproximadamente 85% (Sadoff *et al.*, 2021).

Entre as principais vacinas utilizadas que demonstram uma eficácia, são as baseadas em RNA mensageiro (mRNA), incluindo a BNT162/BNT162b2 (Pfizer-BioNTech) e mRNA-1273 (Moderna). Suas vantagens em relação às vacinas tradicionais, residem principalmente na potencialidade de regulação do sistema imune adaptativo, indução de respostas imunes celulares e humorais, além da agilidade que podem ser desenvolvidas, pois a tecnologia permite que sejam projetadas assim que a sequência genética do vírus é identificada, acelerando o processo de fabricação, apresentando segurança, pois o mRNA viral utilizado é degradado no citoplasma após a produção de proteínas alvo, não havendo integração ao genoma do hospedeiro. Além disso, de acordo com ensaios clínicos realizados em estudos anteriores, ambas as vacinas demonstraram uma eficácia de aproximadamente 95% (Patel *et al.*, 2022; Jamous; Alhomoud, 2023).

As vacinas baseadas em mRNA são capazes de induzir potencialmente uma resposta de ativação de células T CD8⁺ de memória, que persistem por mais de 6 meses após a vacinação. Essas células possuem o papel fundamental de citotoxicidade promovendo a morte do vírus, o mecanismo de ativação ocorre quando os peptídeos antigênicos são apresentados por meio do

MHC de classe I na superfície celular, que são reconhecidos pelas células T CD8⁺ específicas à proteína S. As células T CD4⁺ possuem também um papel auxiliar na resposta adaptativa, diferenciando-se em tipo 1 secretando interleucinas 2 (IL-2) e interferon-gama (IFN-γ), que são responsáveis por ativarem as células T CD8⁺, adquirindo funções efetoras (Chen; Venturi; Munier, 2023).

Os estudos de fase I e II da BNT162 avaliaram a segurança, tolerabilidade e imunogenicidade da vacina. Em adultos saudáveis, os efeitos adversos foram relatados em 50% dos indivíduos que tomaram entre 10-30μg e 58% daqueles em que foram aplicados 100μg, no entanto, dos 45 indivíduos participantes apenas 2 tiveram efeitos adversos graves. Houve aumento dos anticorpos IgG anti-RBD após 7 dias pós-vacinação que teve um *boosting* após 21 dias naqueles que tomaram uma dosagem menor. Os que receberam a dosagem maior não houve diferença entre os intervalos, permanecendo as concentrações elevadas de anticorpos mesmo após 21 dias (Mulligan *et al.*, 2020). Nos estudos de fase III a BNT162 demonstrou 95% de efetividade contra o vírus após 28 dias da primeira dose, 84% dos participantes relataram ter efeitos adversos leves e moderados na primeira dose e 79.4% após aplicação da segunda dose, com durações entre 1-3 dias (Baden *et al.*, 2021).

As formulações bivalentes das vacinas BNT162b2 (Pfizer) e mRNA-1273 (Moderna) foram autorizadas pela *Food and Drug Administration* (FDA) com intuito de conferir uma maior proteção contra as variantes circulantes, tendo a tecnologia responsável por traduzir a proteína S a partir do mRNA da cepa ancestral (Wuhan) e da variante Ômicron (B.1.1.529), incluindo as subvariantes BA.4 e BA.5, com aplicabilidade em dose única de reforço após dois meses do primeiro esquema vacinal. Estudos de monitoramento da segurança dessas vacinas foram realizados em indivíduos com mais de 12 anos que foram liberados para receber a dose, onde se observaram 60,8% de reações adversas sistêmicas e 54.8% reações no local da injeção (Hause *et al.*, 2022). Além disso, estudos para avaliação destas vacinas realizados com pessoas acima de 55 anos e acima de 18 anos que receberam duas doses do primeiro esquema vacinal e uma dose de reforço da vacina monovalente demonstraram, dentre os que receberam a vacina bivalente após um mês, um aumento dos níveis NAbs, comparado aos que receberam apenas o reforço da vacina monovalente. A taxa de soroconversão foi 71,6% para Pfizer e 74,9% Moderna em comparação dos que tomaram monovalente 57% e 53,9% respectivamente. A eficácia relativa da vacina foi investigada na observação das taxas de hospitalizações e consultas ambulatoriais na infecção com SARS-CoV-2, os pacientes que receberam a vacina mRNA-1273 demonstrou redução nessas taxas em comparação com os que tomaram

BNT162b2, sendo a população idosa mais beneficiada (Barda *et al.*, 2023; Kopel *et al.*, 2023; Winokur *et al.*, 2023; Usdan *et al.*, 2024).

No Brasil, a segunda onda de infecções pelo SARS-CoV-2 apresentou ser a mais agressiva no país, a necessidade de implementação de vacinas era viável no contexto para mitigar os casos graves e contenção da infecção (Zeiser *et al.*, 2022). Com isso, o programa de vacinação contra a COVID-19 no Brasil teve o início em janeiro de 2021, as vacinas foram ofertadas pelo Programa Nacional de Imunizações (PNI) e com aprovação e autorização da Agência Nacional de Vigilância Sanitária (ANVISA) para uso emergencial e/ou definitivo, dentre as vacinas aplicadas no país foram a CoronaVac da empresa Sinovac em colaboração com o Instituto Butantan aplicada em duas doses com intervalo de 15 dias, ChAdOx1 e BNT162 da Pfizer com duas doses, porém o intervalo de 40 dias e Janssen com aplicação em dose única, ambas de empresas farmacêuticas. O esquema vacinal envolveu uma estratégia de vacinação em fases, priorizando inicialmente os grupos de risco com comorbidades e profissionais da saúde e, conforme o aumento de disponibilidade das doses, a vacinação foi ampliada para a população em geral (Anvisa, 2024; Brasil, 2024).

Neste contexto, a parceria entre instituições público-privada (PPPs) tornou possível o desenvolvimento, em tempo recorde, de vacinas baseadas em diferentes tecnologias visando a mitigação da mortalidade e redução das ocupações nos centros de saúde, não só no Brasil, mas em todo o mundo. Além disso, o acesso à vacinação para população é oriundo da agilidade e flexibilidade das empresas privadas como, farmacêuticas e de biotecnologias na ampliação da capacidade de testagem de métodos rápidos de diagnósticos, vacinas e fornecimento de equipamentos de proteção individual. Já as instituições públicas, em sua concomitância, têm a função de ampliar a realização de pesquisas clínicas, estudos epidemiológicos, ensaios pré-clínicos aprimorando o conhecimento e acelerando a descoberta de soluções inovadoras no combate a doenças negligenciadas e epidemias melhorando a qualidade de vida da sociedade (Díez-Domingo *et al.*, 2022; Schramm, 2023).

1.5 Doenças alérgicas respiratórias

As alergias respiratórias se constituem em manifestações comumente vistas nas doenças alérgicas. São mediadas pela produção de anticorpos IgE específicos induzido por diferentes alérgenos ambientais, substâncias inofensivas para alguns, mas que podem desencadear respostas exacerbadas a outros, induzindo um perfil de reação de hipersensibilidade do Tipo I, conforme classificação de Gel e Coombs (Gell; Coombs, 1963), termo esse que muitas vezes se confunde à atopia, que consiste na identificação de indivíduos que possuem predisposição

genética ao responder diversos antígenos/alérgenos levando a superprodução de IgE específica (Dispenza, 2019). As doenças atópicas comuns são asma brônquica alérgica, rinite alérgica, dermatite atópica e alergia alimentar (Vaillant *et al.*, 2023). No entanto, pode ocorrer a existência de reações alérgicas que não mediadas por IgE, com a participação da classe de anticorpos IgG alérgenos-específicos, que também podem ser encontrados em altas titulações no soro de pacientes alérgicos, incluindo suas subclasses IgG1 e IgG4 (Feng *et al.*, 2018; Qin *et al.*, 2022).

Estudos dos séculos passados acreditavam que a alergia era resultante de mecanismo ativado mediante uma predisposição genética. No entanto, atualmente, a ciência tem evidenciado que os fatores ambientais podem alterar a epigenética nas células dos indivíduos e ao mesmo tempo possuir um efeito protetor na imunidade. Um exemplo disso é o microbioma, que tem apresentado interesse substancial nas pesquisas para esclarecer o mecanismo de surgimento de alergias por meio de mudanças na dieta e uso precoce de medicamentos que causam redução da diversidade microbiana, levando a doenças inflamatórias crônicas e alérgicas (Zubeldia-Varela *et al.*, 2022; Pantazi *et al.*, 2023).

Além dos fatores genéticos, o ambiente exerce um importante papel na alergia, em particular a exposição alergênica, a etapa de contato do indivíduo através das vias respiratórias superiores por meio da inalação, contato ou ingestão de proteínas alergênicas que são cruciais no desenvolvimento de doenças alérgicas mediadas por IgE e a ocorrência da exacerbação dos sintomas alérgicos frequentemente estão associados à dificuldade na execução de uma profilaxia efetiva para garantir as medidas preventivas de exposição alergênica, o que torna um grande desafio para os pesquisadores na busca de novas estratégias terapêuticas, e para tanto, sendo de suma importância o conhecimento profundo da imunopatogenia bem como da fisiopatologia destas doenças (Khayath *et al.*, 2018; Caraballo *et al.*, 2020).

A exposição a determinados antígenos pode culminar na fase de ativação do sistema imunológico denominado de primeiro sinal, que culmina no reconhecimento antigênico pelas células T CD4⁺ *naïve* através da interação do receptor TCR e complexo antígeno e MHC de classe II, em seguida, na próxima fase ocorre o segundo sinal da co-estimulação destas células com a interação entre as moléculas CD28 (presentes nas células T) e moléculas CD80 e CD86 (presentes nas APCs), que sofrem diferenciação e proliferação. No terceiro sinal ocorre a diferenciação das células T adquirindo os perfis Th1, Th2, Th9, Th17, Th22, Treg (T regulatória) dependendo da produção de citocinas presentes no microambiente. O perfil de citocinas secretadas pelas diferentes subpopulações funcionais é responsável por promover respostas inflamatórias personalizadas para cada tipo (Berker *et al.*, 2017; Sabat *et al.*, 2019).

Neste contexto, durante a fase de sensibilização alérgica, no primeiro contato do indivíduo com o alérgeno, o terceiro sinal decorre da produção da citocina IL-4, que induz a expressão do fator de transcrição GATA-3 em células T CD4⁺, que, além desta, ainda produzem citocinas IL-5, IL-9, IL-10 e IL-13, caracterizando esta subpopulação funcional como células Th2. As citocinas IL-4 e IL-13 serão responsáveis por estimularem células B sintetizar a classe de anticorpo para IgE, que se ligarão nos receptores Fcε presentes em células alvos como basófilos no sangue e mastócitos em tecidos. Na exposição alérgica, os anticorpos IgE podem se ligar de forma cruzada aos epítomos de diferentes alérgenos, desencadeando a ativação das células alvos, consequentemente, resultando na liberação de grânulos contendo mediadores vasoativos pré-formados, como histamina, fatores quimiotáticos para eosinófilos, fatores quimiotáticos para neutrófilos, entre outros. A histamina causará vasodilatação e aumento da permeabilidade capilar, que serão responsáveis pela produção da hiperemia e edema ou hipersecreção, respectivamente, nos brônquios e bronquíolos ocorre a contração da musculatura lisa e produção de muco. Em adição, para agravar o processo inflamatório alérgico, a citocina IL-5 atrai e ativa eosinófilos, característica marcante em doenças alérgicas clássicas. O quadro de sintomas irá depender dos órgãos envolvidos nesta resposta, podendo ocorrer anafilaxia, asma, conjuntivite alérgica, dermatite atópica, rinite alérgica, urticária, entre outros (Kubo, 2017; Taketomi *et al.*, 2017).

1.6 Aeroalérgenos

Os aeroalérgenos são proteínas que possuem um potencial alérgico, suspensos no ar podem desencadear reações alérgicas em indivíduos que respondem de forma exacerbada gerando grandes impactos na qualidade de vida. Os mais comuns são pólen de gramíneas, fungos, ácaros de poeira domiciliar (HDM) e pelos de cão e gato. A exposição a esses alérgenos causa preocupações em algumas regiões, especialmente durante períodos sazonais da estação polínica, fatores ambientais que favorecem o crescimento de fungos e ácaros (Reid; Gamble, 2009; Shamji; Durham, 2017). A manifestação clínica é dependente da exposição das partículas alérgicas, podendo ocorrer pelas vias respiratórias e oculares, ocasionando rinoconjuntivite alérgica, ambas acarretando sintomas característicos de inflamação de mucosa, como prurido, hipersecreção e espirros (Lei; Grammer, 2019).

A prevalência de um aeroalérgenos difere em regiões, dependendo do tipo de clima, e essa distribuição exerce um importante papel na patogênese da asma e rinite alérgica (Katel *et al.*, 2021; Thao *et al.*, 2023; Montoro *et al.*, 2024). Os HDM são os principais causadores dessas doenças no Brasil, devido aos climas tropical e subtropical, com prevalência das famílias

Pyroglyphidae e Echymiopodidae, sendo os principais: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae* e *Blomia tropicalis* (Souza Lima *et al.*, 2018). Estudos anteriores na cidade de Uberlândia, em Minas Gerais, encontraram alta prevalência de indivíduos sensibilizados com alérgenos de HDM, sobretudo das espécies *D. farinae* (Der f 1), em 60-80% das amostras, e *D. pteronyssinus* (Der p 1), em aproximadamente 50% (Sopelete *et al.*, 2000). O indivíduo que possui o interesse de saber qual o alérgeno que, mediante a exposição e sensibilização, desencadeou sintomas de alergias respiratórias podem realizar o teste de diagnóstico para espécies de aeroalérgenos, neste contexto o Teste Cutâneo de Puntura (TCP) é utilizado, sendo uma ferramenta padrão para diagnóstico de doenças alérgicas mediadas por IgE. Para realização do teste, são utilizados extratos comerciais de várias espécies de aeroalérgenos, que são aplicados na superfície da pele do antebraço do paciente, a positividade é observada quando o tamanho da pápula formada é maior que 3 mm de diâmetro (Bousquet *et al.*, 2012). A interpretação do teste deve ser realizada por profissional qualificado com a supervisão de médico alergista, a positividade depende do desenvolvimento de sintomas, seguido de realização de testes de diagnósticos laboratoriais para detecção de IgE específica aos alérgenos (Antunes *et al.*, 2009).

Atualmente vários estudos têm investigado o papel dos expossomas, esse termo se refere a todo tipo de exposição à fatores ambientais pelo indivíduo, ao longo dos anos, tendo influência na homeostase do organismo, que pode estar relacionado com doenças. As alterações climáticas e poluentes ambientais contribuem no agravamento de doenças respiratórias. Neste sentido, estudos investigaram o mapeamento do que nomearam de “expossoma alergênico” dependentes do clima subtropical, em diferentes fenótipos atópicos e observaram que há uma prevalência de exposição simultânea de vários alérgenos de HDM e principais proteínas do alérgeno de pelo de gato (Fel d 1) que estavam associados à produção de IgE em pacientes atópicos e com dermatite atópica (DA) demonstrando a complexidade das doenças atópicas. Esses estudos concluíram que é importante identificar esses complexos alergênicos a nível molecular, principalmente na avaliação clínica, em busca de terapias e diagnósticos personalizados para os indivíduos atópicos e com doenças respiratórias (González-Pérez *et al.*, 2023; Pfirman; Devonshire; Winslow, 2024).

1.7 Asma

A asma atópica é uma doença caracterizada por um processo inflamatório crônico nas vias respiratórias inferiores, envolvendo células do sistema imune, epiteliais, endoteliais e da musculatura lisa. A interação entre as células epiteliais brônquicas com os alérgenos inalantes

é o suficiente para desencadear a expressão de citocinas pró-inflamatórias e o recrutamento e ativação das células imunes, incluindo células dendríticas, linfócitos T *helper*, neutrófilos, basófilos, eosinófilos, mastócitos e macrófagos (Hoffmann *et al.*, 2016; Alobaidi; Alsamarai; Alsamarai, 2021; Komlósi *et al.*, 2022).

Os pacientes acometidos por essa doença possuem como características clínicas as lesões teciduais no pulmão, disfunção do músculo liso e a remodelação das vias respiratórias, o que resulta em hiperreatividade brônquica e obstrução destas vias, somado a uma elevada concentração sérica de IgE alérgeno-específico, expressão aumentada de TSLP e com uma predisposição à produção ampliada das citocinas IL-4, IL-5, IL-9 e IL-13. A remodelação das vias respiratórias nos asmáticos está diretamente associada ao dano tecidual causado pela inflamação crônica, resultando em um reparo desregulado com subsequente obstrução das vias respiratórias e o declínio da função pulmonar de maneira progressiva (Boonpiyathad *et al.*, 2019; Hammad; Lambrecht, 2021).

Os principais sintomas da asma são a dispneia, sibilância, tosse e aperto no peito os quais são desencadeados com a presença de gatilhos, como o contato direto com aeroalérgenos da poeira domiciliar, pólen de plantas de ambiente externo ou infecções virais que devem ser identificados e tratados conforme o nível de sintomas e diagnóstico (Jones; Neville; Chauhan, 2018). Alguns indivíduos atópicos possuem a propensão em desenvolver asma o que pode estar estreitamente correlacionada com as doenças alérgicas, entretanto, indivíduos asmáticos podem não apresentar sintomas alérgicos, assim como indivíduos atópicos podem não desenvolver asma (Gerday *et al.*, 2022).

Os fenótipos associados a doença são a hiper-responsividade brônquica e IgE com níveis elevados. Apesar de todo o contexto clínico e imunológico, vários fatores podem interferir no desenvolvimento da asma, como os externos, no caso dos riscos ambientais com a exposição à poluição do ar, que pode exacerbar os sintomas; comportamentais, o tabagismo que é um elemento preditivo nas crises asmáticas em indivíduos alérgicos e a obesidade que é outro fator desencadeante da doença pois fisiologicamente reduz a mecânica pulmonar com o aumento do peso causando a dispneia e piorando o quadro clínico; os riscos ocupacionais que potencializam o agravamento da asma com progressão diagnóstica à morbidade são os ambientes de trabalho e estudo que os indivíduos são expostos na maior parte do tempo com a presença de sensibilizadores locais que contribuem na sensibilização alérgica, tendo substâncias que possuem alto peso molecular (farinha, gomas, enzimas alimentares, tabaco, proteínas derivadas de látex, alérgenos derivados de ácaros e alérgenos alimentares derivados de frutos do mar) e

de baixo peso molecular (polímeros, anidridos ácidos, metais e substâncias químicas (Peters; Dixon; Forno, 2018; Leynaert *et al.*, 2019; Huang *et al.*, 2020; Bellou; Gogali; Kostikas, 2022).

O desenvolvimento e progressão da asma atópica está diretamente relacionada à predisposição genética em diferentes faixas etárias, pela exposição a diversos fatores ambientais e ao estilo de vida contemporâneo, o que favorece a exposição aos alérgenos e a fatores de risco para asma (Cecchi; D'amato; Annesi-Maesano, 2018). Além disso, infecções virais respiratórias, no início da vida, contribuem para a expressão de mediadores pró-inflamatórios, incluindo a TSLP, o que desencadeia uma cascata de inflamação e predispõe ao desenvolvimento de asma atópica (Welham *et al.*, 2023).

Uma abordagem personalizada para a asma é a presença de endótipos que detectam o tipo de inflamação que conduzem a doença, auxiliando futuros tratamentos por meio de biomarcadores específicos. O Tipo 2-*high* leva o aumento de substâncias pró-inflamatórias, denominadas alarminas: TSLP, IL-25 e IL-33 que são responsáveis em ativar células Th2 que produzem IL-4 que induz os plasmócitos liberarem IgE específica ao alérgeno, as células linfoides inatas do tipo 2 (ILC2), mastócitos, basófilos e eosinófilos também contribuem para o quadro inflamatório, responsável por desencadear sintomas graves nos indivíduos comprometidos (Nakagome; Nagata, 2024). O Tipo 2-*low* é observado em uma pequena porcentagem de pacientes com asma grave, a característica principal é a inflamação neutrofílica e resistência à corticosteroides. Em geral, esse endotipo é marcado por resposta Th1-*high* com a produção de IFN- γ elevada e/ou Th17-*high* caracterizada por níveis aumentados de IL-17a e IL-22, desencadeando a patologia através da deposição de colágeno nas células musculares lisas. Ambas as respostas são responsáveis por ocasionar desregulação nas respostas de células Tregs (Kuruvilla; Lee; Lee, 2019; Akar-Ghbril *et al.*, 2020).

A quantidade de novos casos de asma atópica tem crescido no mundo todo e a Organização Mundial de Saúde estima que existam, atualmente, 300 milhões de casos de asma atópica e, até 2025, esse número pode chegar aos 400 milhões de casos. Ademais, há, pelo menos, 250 mil mortes por essa doença por ano, as quais muitas delas poderiam ser evitadas (Pawankar, 2014). Além disso, na realidade brasileira, o Ministério da Saúde estima que haja 20 milhões de indivíduos vivendo com a asma, o que tem gerado uma alta despesa aos cofres públicos (ASBAI, 2020).

Segundo o Sistema de Informações Hospitalares do Sistema Único de Saúde (SIH-SUS) esse impacto foi de US\$ 52 milhões por ano entre 1992 e 2006, podendo haver o custo de até 18 bilhões de reais caso todos os pacientes tivessem acesso ao tratamento correto. Além do custo financeiro direto, há um alto impacto social ocasionado pela asma no Brasil, visto que

muitos indivíduos são demitidos ou não conseguem ir trabalhar e/ou estudar devido a exacerbação de crises de asma. Dessa forma, fica evidente que a asma atópica gera diversos custos diretos (ida ao médico ou hospital, medicação, exames, etc) e indiretos (prejuízos no ambiente de trabalho e/ou escolar), se tornando um problema não só sanitário, como também, financeiro e social (Damasceno *et al.*, 2012; ASBAI, 2015).

Para avaliação dos sintomas da asma, é utilizado o questionário de avaliação do Teste de Controle da Asma (ACT), sua aplicação possui o intuito de avaliar a percepção do estado dos sintomas por parte do paciente. O questionário é autoaplicável e contém cinco perguntas, sobre a frequência do uso de medicação para alívio, efeito da asma nas atividades cotidianas, qualidade do sono, falta de ar e controle da asma. O uso do ACT permite sua padronização na prática clínica e protocolos de pesquisa que se faz necessário realizar adequadamente a percepção dos sintomas por parte do paciente, direcionando o melhor tratamento além de ser independente de intervenções de avaliação função pulmonar (Roxo *et al.*, 2010). A percepção imprecisa dos pacientes sobre seu real estado sintomatológico pode levar a gravidade da doença além de uso inadequado de medicamentos. Estudos tem demonstrado que pacientes com asma bem controlada foram bem assistidos por meio da boa percepção dos seus sintomas por parte de médicos, outros grupos de pacientes com asma má controlada ou parcialmente controlada relataram uma autopercepção errônea do seu estado (Gebremariam; Sherman; Schluger, 2019; George *et al.*, 2022).

1.8 Rinite Alérgica

A rinite alérgica (RA) é considerada uma condição comum que pode impactar negativamente a qualidade de vida dos pacientes devido aos sintomas serem caracterizados por espirros, congestão nasal, coceira e secreção nasal desencadeando reações mediadas por anticorpos da classe IgE específicos ao alérgeno inalado. Estes alérgenos são oriundos do ambiente externo ou interno que o indivíduo é exposto frequentemente, sendo no trabalho ou casa em ambientes fechados com pouca ventilação que são encontrados comumente ácaros e outros insetos e/ou lazer como passeios ao ar livre que são mais susceptíveis a presença de pólen de plantas (Mortada; Kurowski, 2023). A exposição ambiental dos indivíduos pode ser somente o gatilho para desenvolvimento da RA em um paciente que já possui uma predisposição genética à doença. Os fatores de risco para desenvolvimento da RA são o uso de antibióticos, poluição do ar (pessoas que vivem em grandes capitais), exposição à animais domésticos e de fazenda, tabagismo materno e paterno e atividade física vigorosa na adolescência (Bousquet *et al.*, 2020).

Os mecanismos fisiopatológicos da RA são compreendidos por meio da exposição alérgica no desencadeamento de reações alérgicas nasais. A mucosa nasal é a primeira linha de defesa contra agentes externos infecciosos oriundos do ar do trato respiratório do indivíduo. Os alérgenos podem prejudicar a integridade dessa mucosa que com suas atividades proteolíticas comprometem a barreira do epitélio podendo também ativar receptores de superfície nas células, liberando alarminas que ativam células ILC2 que produzem eficazmente citocinas inflamatórias como IL-5, IL-13 e IL-4 que são responsáveis por iniciar a cascata de ativação de respostas imunes adaptativas do Tipo 2 e *switch* de classe de anticorpos IgE (Schleimer; Berdnikovs, 2017; Roan; Obata-Ninomiya; Ziegler, 2019; Bernstein *et al.*, 2024).

A sensibilização alérgica na rinite alérgica é facilitada por um aeroalérgeno que é capturado pelas APCs que liberam as proteases ativando células do epitélio nasal a produzirem TSLP, IL-33 e IL-25 que possuem efeitos diretos na ativação de células ILC2 e células T de perfil Th2. As ILC2 podem possuir um papel modulador capaz de polarizar células T *naïve* para Th2 produtoras de IL-13 necessárias para o recrutamento de células dendríticas para os nódulos linfáticos. As células de perfil Th2 ativadas pelo alérgeno produzem IL-4 e IL-13 que são secretadas para manutenção das células Th2 e recrutamento de células T CD4⁺ expressando CD40L que juntos promovem a troca de classe dos linfócitos B na produção de anticorpos IgE. Os anticorpos IgE são responsáveis por ligarem no seu próprio receptor de alta afinidade (FcεRI) localizado na superfície de mastócitos e basófilos que são induzidos a liberar grânulos como a histamina que atua no aumento da inflamação nas vias nasais (Eifan; Durham, 2016; Albloushi; Al-Ahmad, 2024).

A rinite alérgica é presumida e apresentada como sazonal ou conhecida como febre do feno, sendo desencadeada por uma gama de variados alérgenos externos. A rinite alérgica perene é induzida por alérgenos internos presentes em ambientes fechados, ácaros, fungos, insetos e pelos de animais. É classificada de acordo com sintomas clínicos da doença: leve/moderada/grave e em casos particulares de pacientes alérgicos exclusivamente ao HDM. Os indivíduos com rinite alérgica perene apresentam também sintomas clínicos que são frequentemente expostos a alérgenos, podendo ocorrer crises durante uma semana ou menos de 4 semanas consecutivas (Wise *et al.*, 2018; Bernstein *et al.*, 2024).

1.9 Alergias respiratórias e COVID-19

Desde a descoberta de que o SARS-CoV-2 afeta fortemente o sistema respiratório, muitos grupos de pesquisa têm se preocupado se as doenças alérgicas respiratórias podem piorar pelo novo coronavírus. Alguns estudos foram realizados para investigar se as doenças alérgicas

poderiam ser consideradas um fator de risco para COVID-19, no entanto, essa associação ainda é controversa (Guan *et al.*, 2020; Aveyard *et al.*, 2021).

Neste contexto, estudos anteriores questionaram se as características da alergia podem estar associadas ao um potencial de redução da gravidade da COVID-19, pois grandes estudos epidemiológicos observaram a baixa na internação de indivíduos infectados no início da pandemia com histórico de asma alérgica, em comparação a indivíduos com asma grave não relacionada a alergia (Wu; Mcgoogan, 2020; Kocatürk *et al.*, 2023). Essa hipótese levou vários pesquisadores a identificarem o papel da expressão da ACE2 nos indivíduos com doenças alérgicas, visto que esse receptor é responsável pela entrada do SARS-CoV-2 durante a infecção (Scialo *et al.*, 2020; Carr; Kraft, 2022). Desta forma, examinaram amostras das vias respiratórias de pacientes com asma e rinite alérgica para sequenciamento do RNA extraído das células epiteliais pulmonares. Os resultados demonstraram que a presença de alergia respiratória e a exposição a alérgenos estão associados a reduções significativas na expressão da ACE2, sugerindo a descoberta de um potencial mecanismo na redução da replicação viral e gravidade da doença (Jackson *et al.* 2020).

A modulação da expressão de ACE2 pode estar relacionada com o tipo de resposta inflamatória encontrada em indivíduos com atopia. A infecção por SARS-CoV-2 induz resposta de perfil Tipo 1 com envolvimento de citocinas pró-inflamatórias como IFN- γ e tempestade de citocinas, que por outro lado nas respostas alérgicas, o perfil Tipo 2 é prevalente com o envolvimento de citocinas IL-4 e IL-13 (Adir *et al.*, 2021; Su *et al.*, 2024). A inflamação elevada de Th2 pode reduzir o risco de infecção do vírus. Estudos relataram que os endótipos da asma também interferem na gravidade da COVID-19, indivíduos asmáticos que exibem T2-*low* por consequência possuem expressão aumentada de ACE2 devido ao aumento exacerbado junto a infecção de citocinas pró-inflamatórias, além de comorbidades que podem afetar esse grupo, como obesidade, diabetes e inflamações metabólicas que podem contribuir para o aumento de sintomas adversos da infecção (Dounce-Cuevas *et al.*, 2023).

Em indivíduos atópicos com sintomas graves, observou-se a supressão de IFN- γ em células dendríticas induzidas pelo receptor *Toll-like* 9 após estimulação viral por SARS-CoV-2. Isso ocorre devido ao aumento significativo de anticorpos IgE que pode comprometer a resposta antiviral desses indivíduos causando sua ineficiência na eliminação do vírus (Adir *et al.*, 2021; Carli *et al.*, 2021). Uma solução para a gravidade da asma induzida por vírus é o tratamento com Omalizumab, um anticorpo monoclonal anti-IgE que induz o aumento de

células dendríticas produtoras de IFN- γ e reduz a expressão do receptor Fc ϵ RI, melhorando a eficiência das repostas frente ao vírus e na diminuição da gravidade da asma (Gill *et al.*, 2018).

1.10 Exercício físico e COVID-19

O estilo de vida de algumas pessoas enfrentou transformações durante o período de isolamento social na quarentena da COVID-19, resultando em hábitos poucos saudáveis, como o sedentarismo, aumento da ingestão de alimentos por recompensa, restrição de acesso a academias e parques, além do uso de medicamentos como medida preventiva contra a doença. Essas mudanças foram acompanhadas por transtornos emocionais, que estão diretamente ligados a redução na prática de exercícios físicos e ao consumo de alimentos saudáveis (Pandey *et al.*, 2023). Algumas dessas atitudes, a longo prazo, fornecem uma carga imensa para doenças cardiovasculares, obesidade, hipertensão, diabetes, síndrome metabólica e a redução da sensibilidade a insulina (Kinoshita *et al.*, 2023). A atividade física é responsável por desempenhar um papel fundamental na saúde do indivíduo, melhorando a qualidade de vida, reduzindo nível de gordura, aumentando a massa corpórea e contribuindo primordialmente na resposta do sistema imunológico para eliminação das infecções virais. Estudos comprovam que o exercício de intensidade moderada é válido neste caso, pois possui atividade antipatogênica e auxilia o trato respiratório na diminuição de doenças, incluindo a COVID-19 (Hammami *et al.*, 2020; Polero *et al.*, 2020; Laddu *et al.*, 2021).

O sedentarismo é responsável por reduzir o gasto energético e promover o aumento da ingestão de alimentos, principalmente na quarentena, com o fácil acesso da comida, tanto em lares domiciliares e/ou aplicativos de celular, levando ao aumento de transtornos de saúde mental, como a ansiedade que estão correlacionadas com aumento de mídias digital principalmente em jovens (Musa; Elyamani; Dergaa, 2022). O consumo de informações com propaganda de *fast-food* por meios televisivos ou por smartphones também contribuem no aumento calórico destes alimentos que fornecem sensações de prazer e plenitude momentânea. Estudos realizados confirmam que uma dieta restrita em calorias acompanhada de inatividade física é importante na situação do isolamento social, pois auxilia na redução de distúrbios do sono, melhorando a atividade dos hormônios tireoidianos e diminuindo espécies reativas de oxigênio (ROS) que previne o envelhecimento precoce (López-Otín *et al.*, 2016; Redman *et al.*, 2018; Martinez-Ferran *et al.*, 2020; Woo *et al.*, 2022).

A atividade física leva a benefícios protetores em pacientes com sintomas leves da COVID-19, sugerindo que indivíduos fisicamente ativos possuem menores chances de serem diagnosticados com a doença. Assim, foi necessário o incentivo do exercício durante o

isolamento social para promoção da saúde e fortalecimento do organismo contra infecções virais (Zhang *et al.*, 2020b; Yang *et al.*, 2022). A modulação da resposta imune está relacionada a atividade física dependendo de fatores como a frequência, intensidade, regularidade e tipo de esforço, como por exemplo em exercícios físicos moderados observa-se a estimulação da imunidade celular, no entanto os exercícios de alta intensidade provocam diminuição dessa imunidade. A produção de citocinas depende do Tipo de exercício e seus níveis de intensidade, no caso da musculação, o efeito da contração muscular aumenta a liberação de citocinas anti-inflamatórias e pró-inflamatórias variando de acordo com volume de massa exercida durante a contração, além disso estudos tem observado que a intensidade do exercício contribui para benefício das condições pós-covid (Docherty *et al.*, 2022; Thirupathi *et al.*, 2023).

Neste contexto, o processo de modulação imunológica por meio do exercício pode auxiliar no combate de infecções por SARS-CoV-2 provocando mudanças positivas na vida dos pacientes com COVID-19 podendo levar o aumento da proteção vacinal, redução de marcadores inflamatórios de obesidade, atenuar a neutrofilia nas lesões pulmonares, também causando melhorias imunometabólicas no controle de distúrbios de coagulação através do estímulo do eixo vasoconstritor (Simpson; Katsanis, 2020; Da Silveira *et al.*, 2021; Wittmer *et al.*, 2021). Estudos relataram a relação entre o desenvolvimento de casos graves da doença em indivíduos com estilo de vida sedentário, outras evidências sugerem que a prática regular do exercício físico é um dos fatores que regulam a tempestade de citocinas e reduzem as sequelas causadas pós-COVID-19, levando a maior proteção contra a doença e menor risco de gravidade (Fernández-Lázaro *et al.*, 2020; Jimeno-Almazán *et al.*, 2021).

A prática de exercícios físicos também pode contribuir na modulação da resposta imune em indivíduos vacinados, estudos clínicos investigaram a associação entre o aumento da eficácia da vacina contra influenza após exercício físico aeróbico a longo prazo em comparação com indivíduos que realizam o exercício agudo, apenas em curto prazo (Dinas *et al.*, 2022). A eficácia da vacina tetravalente contra o vírus da gripe foi observada em atletas com aumento de células T CD4⁺ após uma semana da vacinação comparado aos não atletas (Ledo *et al.*, 2020). Além disso, idosos sedentários que eram exercitados possuíam níveis aumentados de anticorpos IgM e IgG específicos a influenza em relação aos inativos, idosos ativos também apresentaram níveis baixos de quimiocinas e aumento da expressão de genes associados a fagocitose (Wong *et al.*, 2019).

As vacinas contra a COVID-19 demonstram ter uma excelente eficácia no aumento da resposta imune, com a produção de anticorpos específicos e células T de memória para proteção da infecção (Chen; Venturi; Munier, 2023). Nesse sentido, o exercício físico pode desempenhar

um papel importante na modulação da resposta imune após a vacinação. A comparação da eficácia vacinal e a condição física foram abordadas anteriormente por autores, onde indivíduos regularmente ativos e exercitados antes da vacina obtiveram a resposta melhorada, entretanto se esses mesmos indivíduos reduzissem a atividade física poderia comprometer as respostas vacinais. Em um estudo com indivíduos sedentários que treinaram minutos antes da vacinação, observou-se uma maior eficácia da vacina comparado aos indivíduos totalmente sedentários que não realizaram nenhum exercício anteriormente, havendo redução na eficácia após-vacinação. (Bortolini *et al.*, 2022).

Os processos que melhoram a eficácia das vacinas em resposta ao potencial adjuvante do exercício físico, são mediados por respostas imunes celulares e moleculares, com envolvimento de diversas citocinas e subclasses de anticorpos neutralizantes, que até o momento ainda não foram avaliadas no contexto das vacinas contra SARS-CoV-2 (Bortolini *et al.*, 2022).

1.11 O papel das adipocinas no exercício físico

Existem citocinas específicas envolvidas na inatividade e atividade física que devem ser avaliadas como parâmetro, as adipocinas desempenham um papel essencial na regulação da homeostase, imunidade e metabolismo do organismo, secretadas pelos adipócitos, sua desregulação pode causar distúrbios relacionados à obesidade (Clemente-Suárez *et al.*, 2023). As funções anti-inflamatórias e pró-inflamatórias dessas citocinas são geralmente mediadas por células imunes do tecido adiposo que sofrem a influência de seus estímulos, por exemplo em condições normais, as células Th2 promovem a homeostase da glicose contribuindo para o aumento da sensibilidade à insulina nos adipócitos, ativando assim o tecido adiposo marrom, conhecido por armazenar energia em pequenas gotículas lipídicas. Por outro lado, em casos de inflamação, ocorre a ativação do tecido adiposo branco, ativando vias pró-inflamatórias e inibindo a liberação de citocinas anti-inflamatórias (Pham; Nguyen; Park, 2023; Wang; Zhang; Li, 2023).

A leptina possui um papel pró-inflamatório relacionado com o aumento da adiposidade, contribui na comunicação entre o estado nutricional e no eixo hipotálamo por meio de receptores de sinalização, quanto maior a sinalização hipotalâmica menor a ingestão de nutrientes e maior gasto energético. A modulação imune pelo aumento da leptina ocorre com a ativação de células T CD4⁺ com produção de citocinas como IFN- γ e IL-2, provocando a diminuição da produção da citocina IL-4 de perfil Th2, Tregs, inibição de macrófagos M2,

aumento de TNF- α e IL-6, todos esses mecanismos favorecem essa adipocina ser um potencial marcador de obesidade (Ouchi *et al.*, 2011; Kiernan; Maciver, 2020).

A resistina está envolvida também no processo de obesidade, resistência insulínica e comorbidades, possuindo um efeito pró-inflamatório mediado pela ligação ao receptor *Toll-like* 4 e ativação de NF-kB em macrófagos através das vias JNK e p38MAPK, que por sua vez, desencadeiam inflamações que estão relacionadas com as doenças metabólicas (Kirichenko *et al.*, 2022). Além disso, demonstrou capacidade de neutralizar os efeitos anti-inflamatórios da adiponectina sobre as células endoteliais vasculares, favorecendo a adesão leucocitária, afetando o sistema cardiovascular e aumentando a permeabilidade do endotélio (Ouchi *et al.*, 2011; Acquarone *et al.*, 2019).

A adiponectina é a citocina mais abundante em níveis séricos, é secretada pelos adipócitos e desempenha um papel na prevenção da esteatose e fibrose hepática. Além disso possui ação anti-inflamatória, termogênica, lipolítica e de oxidação de ácidos graxos no músculo esquelético (Choi; Doss; Kim, 2020). Entretanto, níveis baixos estão relacionados com doenças crônicas como obesidade, diabetes tipo 2 e aterosclerose (Clemente-Suárez *et al.*, 2023). A citocina IL-10 é induzida pela adiponectina para diminuição de citocinas inflamatórias como a IL-6, além de aumentar a sensibilidade insulínica na captação da glicose, reduzindo a produção de ROS e inibindo a ativação da via MAPK responsável pela proliferação celular (López-Ortega *et al.* 2022).

Os efeitos do exercício físico na modulação das adipocinas tem sido investigado. A diminuição da leptina foi observada em indivíduos saudáveis com protocolo de exercícios de mais de 60 minutos, associado ao aumento de gasto energético (Bouassida *et al.*, 2010). Em outro estudo, com um treinamento de curta duração com menos de 12 semanas, não foi capaz de alterar significativamente os níveis de leptina. Os níveis de TNF- α e IL-6 também foram reduzidos após o treinamento físico que atua como um efeito imunomodulador natural na síndrome metabólica (Golbidi; Laher, 2014). Os níveis de adiponectina em alguns estudos permaneceram inalterados com a intervenção de exercícios intervalados em indivíduos obesos, mesmo com perda de peso existente (Ouerghi *et al.*, 2022).

A avaliação da modulação das adipocinas em relação ao exercício físico e vacinação para COVID-19 é de extrema importância pois essas moléculas participam dos processos de regulação do metabolismo, inflamação e função imunológica. Além disso, a influência das adipocinas na resposta imune pode impactar na eficácia do exercício como uma intervenção terapêutica para condições inflamatórias. Portanto, compreender como o exercício modula as

citocinas pode fornecer o desenvolvimento de estratégias mais eficazes de promoção da saúde e prevenção de doenças.

2. Objetivos

2.1 Objetivo geral

Avaliar a segurança e resposta imune vacinal em uma coorte de indivíduos imunizados com vacinas para COVID-19 baseadas em vetor viral, mRNA e/ou vírus inativado, considerando presença de atopia rinite e asma, bem como o nível de atividade física.

2.2 Objetivos específicos

- a)** Investigar o perfil de segurança quanto aos efeitos adversos frente às diferentes vacinas contra a COVID-19;
- b)** Avaliar a prevalência de anticorpos neutralizantes (NAb) específicos para SARS-CoV-2 em indivíduos vacinados e não vacinados com ou sem infecção recente com foco no uso de uma plataforma de *point-of-care* baseado em imunocromatografia de fluxo-lateral;
- c)** Avaliar o perfil de modulação da inflamação entre grupos de indivíduos vacinados praticantes (ativos) e não praticantes (sedentários) de atividades físicas;
- d)** Avaliar a modulação da resposta inflamatória entre grupos de indivíduos atópicos com sintomas de rinite alérgica praticantes (ativos) ou não praticantes (sedentários) de atividade física.

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3. Atopia e perfil de segurança das vacinas de COVID-19

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3.1 Manuscrito publicado

Distinct Adverse Reactions to mRNA, Inactivated Virus, and Adenovirus Vector COVID-19 Vaccines: Insights from a Cohort Study on Atopic and Non-Atopic Subjects in Brazil

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Abstract: The emergence of COVID-19 caused by SARS-CoV-2 prompted an unprecedented global response to develop vaccines at an accelerated pace. Messenger RNA (mRNA) and adenovirus vector vaccines emerged as the frontrunners in global immunization efforts, significantly reducing hospitalization, severity, and mortality, supplemented by inactivated virus-based vaccines in developing countries. However, concerns regarding adverse effects, including allergic reactions, have been raised. This study aimed to investigate the adverse effects following COVID-19 vaccination, particularly in atopic and non-atopic individuals. A cohort of 305 volunteers receiving BNT162, ChAdOx1, or CoronaVac vaccines were assessed based on a Skin Prick Test (SPT), specific IgE levels, and clinical history of asthma and rhinitis. Adverse effects were self-reported and scored across the different vaccination shots. The results indicated a notable presence of mild adverse effects following the first and third doses, regardless of vaccine type. ChAdOx1 recipients experienced more adverse effects compared to those receiving BNT162 and CoronaVac, including headaches, muscle pain, fever, chills, nausea, and flu-like symptoms. Atopic individuals receiving ChAdOx1 reported more adverse effects, such as muscle pain, fever, and chills, compared to non-atopic individuals. Conversely, headaches were more frequently reported in non-atopic individuals receiving BNT162 compared to atopic individuals. No anaphylaxis or allergic reactions were reported, indicating valuable evidence supporting the safety of COVID-19 vaccination in individuals with respiratory allergies. This study highlights the importance of understanding vaccine-related adverse effects, particularly in vulnerable populations, to inform vaccination strategies and address safety concerns in global immunization campaigns.

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1. Introduction

Cases of COVID-19, caused by the SARS-CoV-2 virus, were initially reported in December 2019 in Wuhan, China, and subsequently spread globally [1]. Given the swift increase in infection cases, the World Health Organization (WHO) declared it a Public Health Emergency of International Concern (PHEIC) in January 2020 [2], and this status remained until May 2023. During this stage, several vaccine candidates started to be developed and tested at a never-before-seen scale to mitigate severe cases [3]. Also, considering the escalating global SARS-CoV-2 infection rates, international alliances were formed to promptly organize resources in order to accelerate vaccine production [4,5].

In addition to conventional technologies, the COVID-19 pandemic catalyzed advancements in novel vaccine platforms [6]. The BNT162 mRNA vaccine, developed by Pfizer–BioNTech, and the ChAdOx1 adenoviral vector vaccine, developed by the University of Oxford–AstraZeneca, were the initial vaccines endorsed by the World Health Organization (WHO) for emergency deployment [7]. They have predominantly been adopted worldwide, complemented by the administration of other vaccines, such as the inactivated virus vaccine CoronaVac (Sinovac), which has primarily been distributed in low- and middle-income nations [8,9]; together, they markedly reduced the infection rates, severity, and mortality, preventing millions of deaths [10].

The activation of the immune system provided by T regulatory cells and balance between Type 1 and Type 2 immune responses is crucial for individual protection induced by both natural infections and vaccination. Clinical trials and life-real studies demonstrated that the antibody response induced by the COVID-19 vaccines involves the production of IgG, particularly IgG1 and IgG3, and Type 1 cytokines, such as IFN- γ and TNF- α , which is mediated by CD4⁺ and CD8⁺ T cells [11–13]. A wide spectrum of adverse effects has been documented across all the COVID-19 vaccine formulations, including vaccine-related symptoms or allergic reactions. These effects span from common mild symptoms including local pain, fever, and headaches to anaphylaxis, which represents the most severe form of reaction [14]. Although rare, cases of allergic reactions to vaccines have been the focus of many studies [15]. A hypothesis that individuals with pre-existing respiratory allergy might have a higher likelihood of developing anaphylactic or non-anaphylactic responses post-COVID-19 vaccination has been considered [16–18]. A tolerance study with the BNT162 mRNA vaccine conducted by Nittner-Marszalska et al. in 2021 [19] reported a higher duration of systemic adverse effects in allergic patients in addition to a higher frequency of local reactions, headaches, and nausea, as was described elsewhere [20]. An exacerbation of the clinical picture of asthma has been reported after vaccination with an inactivated virus-based COVID-19 vaccine [21], but there are limited studies with a large number of patients focused on respiratory allergies as a side effect. Although some of these observational studies have suggested an association between a previous history of allergy and adverse effects related to COVID-19 vaccination, the mechanism underlying these reactions is still not very clear and it should be explored.

The term atopy is employed to denote the genetic tendency to produce IgE against a small quantity of allergens, typically harmless environmental proteins, followed by a Type 2 immune response [22]. This condition may predispose individuals to the development of allergic diseases, including gastrointestinal disorders, atopic dermatitis, asthma, and rhinitis, among others. A diagnosis of atopy relies on an assessment of specific IgE and/or positivity to a Skin Prick Test (SPT). However, the presence of IgE itself does not indicate an allergy, as allergic responses may also be mediated by other immune components, such as specific IgG, innate immune cells, C3a/C5a complement anaphylatoxins, and cytokines. Consequently, in clinical practice, individuals with an allergy may be categorized as non-atopic if conventional diagnostic tests for IgE yield negative outcomes [23].

Asthma and rhinitis symptoms may be triggered by inhalant allergens from pollen and non-seasonal sources, such as house dust mites, mold, and pets, which elicit both local and systemic immune-mediated inflammation [24]. The most recent classifications for asthma and rhinitis endotypes include upstream and downstream biomarkers, based on omics signatures for IgE, cytokine profiles, neutrophil/basophil populations, and other inflammatory factors [24–26]. However, although this approach is reliable for endotype and phenotype differentiation, the specific IgE assessment still represents the state of the art for atopy diagnosis.

In atopic patients with respiratory allergy, it has been demonstrated that specific IgE can downregulate Type 1 immune response to pathogens. A lack of IgG against infectious agents can be

substantially attributed to IgE-mediated immune responses in atopic subjects with higher levels of IgE against *Dermatophagoides farinae* and *D. pteronyssinus*, two of the main house dust mite species that cause respiratory allergy [27]. In the context of COVID-19, an observational study has elucidated that atopic subjects with specific IgE reactivity to house dust mite antigens exhibit a more favorable disease prognosis. This was coupled with the observation of an immune response predominantly orchestrated by interleukin-13 (IL-13), a potent Type 2 cytokine, suggesting a protective immunological mechanism within this population. Notably, there was no evidence of cross-reactivity between these allergens and SARS-CoV-2 spike protein. Furthermore, increased expression of IL-13 was discerned in these patients after mRNA vaccination, while the levels of specific IgE remained elevated compared to non-atopic individuals [28]. To date, investigations into the potential impact of house dust mite-specific IgE on the occurrence of adverse effects following COVID-19 vaccination have yet to be undertaken.

In this study, we aimed to investigate the safety profile of mRNA, inactivated virus, and adenovirus vector-based COVID-19 vaccines in atopic and non-atopic individuals. The rationale for this research stems from the growing concern over potential adverse effects of COVID-19 vaccines, particularly in populations with underlying allergy conditions. By comparing the incidence and severity of adverse events between subjects with or without atopy, we sought to elucidate any differences in vaccine safety profiles based on allergic status. Understanding these differences is crucial for informing vaccination strategies and mitigating risks in vulnerable populations.

2. Materials and Methods

2.1. Study Design

To investigate if individuals with atopy and a clinical history of respiratory allergy exhibit distinct adverse reactions following COVID-19 vaccination compared to non-atopic individuals, we used a cohort of regular patients, alumni, and hospital staff, who were recruited by an allergy service in Brazil. For atopic/non-atopic classification, they were evaluated for immediate hypersensitivity and specific IgE levels.

The study was based on the Brazilian Vaccination Program for COVID-19 in adults, started in January 2021, with a vaccine schedule consisting of two doses (shot 1 and shot 2, homologous) administered at 8-week intervals for monovalent BNT162 and ChAdOx1 and 28 days for CoronaVac. A heterologous booster dose (shot 3) was included 16 weeks after shot 2. The research was approved by the local ethics committee (Protocol CAAE-50001421.7.0000.5152 CEP/UFU) and informed consent was obtained from all participants prior to their inclusion in the study.

The study was conducted at the Clinics Hospital of the Federal University of Uberlândia, southeastern region of Brazil, with 305 volunteers (18–50 years old) who received BNT162, ChAdOx1, or CoronaVac vaccines between July 2022 and September 2023. Demographic data, including age and sex, along with vaccine-related information, such as the date of the shots, adverse effects, allergic reactions, and type of vaccine administered, were collected as part of the study protocol. The participants were free to report any adverse effects they experienced without limitations or pre-defined options and the answers were categorized. An adverse effect score was determined as the cumulative number of symptoms reported.

Atopic individuals were diagnosed by a positive SPT and/or the presence of house dust mite-specific IgE and those with negative outcomes for both tests were considered non-atopic. The prevalence of rhinitis and asthma was determined by RCAT (Rhinitis Control Assessment Test) and ACT (Asthma Control Test) clinical questionnaires, although these features were not used to determine atopy status. Individuals who were being treated with corticosteroid, antihistamine, or immunosuppressive medication were excluded from the study.

2.2. SPT with Airborne Allergens and *D. farinae*-Specific IgE ELISA

SPT was conducted using house dust mite (*Dermatophagoides farinae*, *D. pteronyssinus*, and *Blomia tropicalis*), dog (*Canis familiaris*), and cat dander (*Felis catus*) allergen extracts (FDA Allergenic, Rio de Janeiro, Brazil) [29]. A wheal diameter ≥ 3 mm after 15 min was considered positive. Serum samples were used to detect *D. farinae*-specific IgE by an indirect ELISA [30]. Briefly, high-affinity microplates were coated with 40 $\mu\text{g/mL}$ *D. farinae* extract for 18 h at 4 °C and blocked with phosphate-buffered saline/0.05% Tween (PBS-T) with 1% Bovine Serum Albumin (BSA). Serum samples (1:2) were diluted

in PBS-T-BSA and incubated at 37 °C for 2 h, followed by incubation with biotinylated anti-human IgE and streptavidin–peroxidase conjugate (1:1000) at room temperature. The reaction was developed by adding 0.01 M 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) and the absorbance values were determined at 405 nm. The results were expressed as an ELISA index (EI) score, as described elsewhere [31]. EI $\geq$ 1.2 was considered positive.

2.3. Statistical Analysis

The statistical significance of differences based on sex, age, and presence of rhinitis and/or asthma were assessed using Student's *t*-tests, Chi-square tests, or Fisher tests, when applicable. Differenced among the vaccine shots were compared using Kruskal–Wallis tests followed by the Dunn's multiple comparison test, with $p < 0.05$ considered to be statistically significant. All statistical analyses were conducted using Prism 9.4 (GraphPad, Boston, MA, USA).

3. Results

3.1. Atopic and Non-Atopic Groups

The subjects were divided in atopic and non-atopic groups, based on SPT and/or specific IgE outcomes. From the 305 people who joined the study, a slightly higher percentage (54.4%) were atopic (Table 1). Although all the volunteers were 18 to 50 years old, the mean age was 30.7 years in the atopic group and 35.0 years in the non-atopic group. In both the atopic and non-atopic groups, female participants predominated at 62.1% and 73.3%, respectively. Although allergic symptoms were not considered for atopy definition, the vast majority of the atopic group (69.8%) reported rhinitis symptoms and even among the non-atopic participants, we found that 38.2% of the patients had rhinitis symptoms. In addition, in the atopic group, only 0.6% reported asthma whereas 9.6% had respiratory allergies. In the non-atopic group, the number of asthmatics was slightly higher (0.7%), but not when associated with rhinitis (2.8%).

In the SPT, the mean wheal size in the atopic group was 5.5 mm for *D. farinae*, 4.8 mm for *D. pteronyssinus*, and 3.6 mm for *B. tropicalis*, followed by 3.9 mm for cat dander and 3.7 mm for dog extracts. All participants in the non-atopic group had negative results in this test.

Regarding *D. farinae*-specific IgE levels, as expected, the atopic subjects reached higher EI values compared to the non-atopic group (2.4 vs. 0.7, $p < 0.0001$). The positivity threshold was set to 1.2 to avoid biased results.

Table 1. Demographic and clinical characteristics of the subjects.

Characteristic	Atopic ¹	Non-Atopic ¹	Total	<i>p</i>
Participants [n (%)]	166 (54.4%)	139 (45.6%)	305	-
Male [n (%)]	63 (37.9%)	37 (26.6%)	100	0.0381
Female [n (%)]	103 (62.1%)	102 (73.3%)	205	
Age (years, mean)	30.7	35.0	-	0.0240
Allergic rhinitis [n (%)]	116 (69.8%)	53 (38.2%)	169	0.4819
Asthma [n (%)]	1 (0.6%)	1 (0.7%)	2	
Allergic rhinitis and asthma [n (%)]	16 (9.6%)	4 (2.8%)	20	
<i>D. farinae</i> wheal size (mm, mean)	5.5	0	-	0.0001
<i>D. farinae</i> -specific IgE (mean)	2.4	0.7	-	0.0001

¹ Atopic/non-atopic subjects were classified based on SPT and *D. farinae*-specific IgE levels.

3.2. Adverse Effects of the COVID-19 Vaccines

All individuals reported at least one adverse effect following COVID-19 vaccination, although they were predominantly mild. No allergic, anaphylactic, or other severe reactions were reported. All adverse effects were compared over the three shots. The first and third shots had higher adverse effect mean scores (1.04 for shot 1 and 1.06 for shot 3) compared to the second shot (0.76, $p < 0.05$) when all vaccines were analyzed (Figure 1A).

We decided to compare the different vaccines independently for each shot to determine if any vaccine had a greater impact on the overall adverse effects data. In the first shot, both the BNT162 and ChAdOx1 vaccines showed no differences between the mean scores (1.6 vs. 1.05, respectively; $p =$

0.3851). Despite this, both had higher mean adverse effects scores compared to CoronaVac (0.36, $p < 0.0001$) (Figure 1B).

In the second shot, BNT162 elicited a higher mean score (1.07) compared to ChAdOx1 (0.69, $p < 0.05$) and CoronaVac (0.39, $p < 0.0001$). However, there was no difference between the mean adverse effect score of ChAdOx1 and CoronaVac ($p = 0.22$) (Figure 1C). Surprisingly, no statistical difference was found between the mean adverse effect scores for the third shot for all vaccines. Nevertheless, it is noteworthy that there was a subtle decrease in subjects who received CoronaVac (Figure 1D).

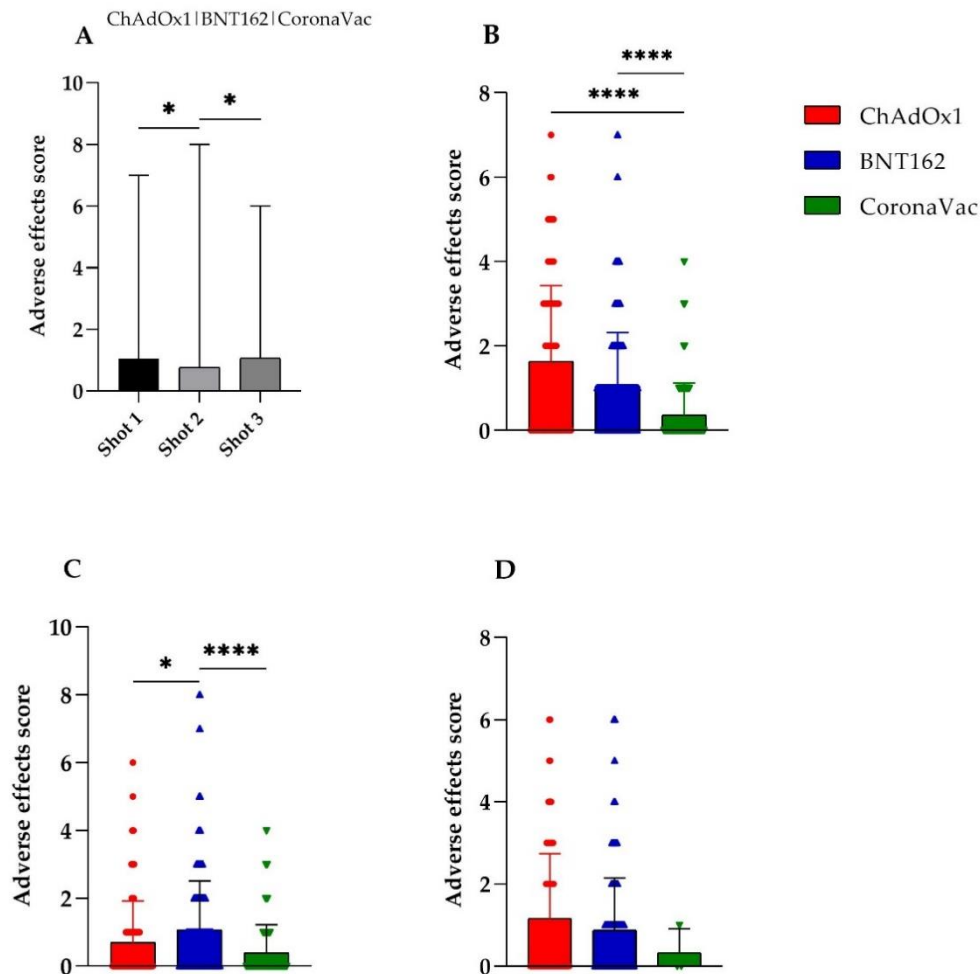


Figure 1. Comparison of the adverse effect scores of the BNT162, ChAdOx1, and CoronaVac vaccines for COVID-19 among (A) shots 1, 2, and 3; (B) shot 1 only; (C) shot 2 only; (D) shot 3 only. * $p < 0.05$; **** $p < 0.0001$.

Therefore, we aimed to investigate if a specific shot of each of these vaccines had a greater impact on the mean values of adverse effects. Figure 2 illustrates the adverse effects after the administration of each vaccine. Notably, only the ChAdOx1 vaccine induced a higher incidence of adverse effects in the first shot (1.63) compared to the second shot (0.69, $p < 0.001$). In contrast, there was no significant difference when compared to the third shot (1.16, $p = 0.1655$), and the same was observed between the second and third shots ($p = 0.1575$) (Figure 2A). On the other hand, the BNT162 and CoronaVac vaccines did not show significant differences in the average symptom score across the vaccination shots (Figure 2B and 2C, respectively).

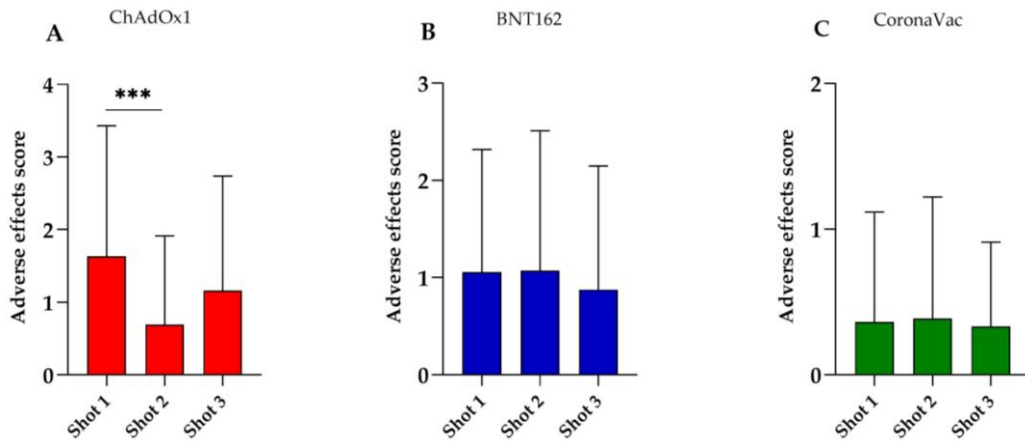


Figure 2. Adverse effect score distribution of (A) ChAdOx1, (B) BNT162, and (C) CoronaVac vaccines for COVID-19. The score was calculated as the cumulative number of adverse effects, ranging from 1 to 4. *** $p < 0.001$.

We also aimed to investigate differences in symptoms associated with the vaccines; then, we focused our analysis on the first shot, which had the largest sample of people available. We assessed the following symptoms: local pain at the injection site, headache, muscle pain, fatigue, fever, chills, enlarged lymph nodes, nausea, and flu-like symptoms (Table 2).

The patients who received the BNT162 vaccine reported higher levels (49.6%) of local pain compared to those who received the ChAdOx1 (31.9%) and CoronaVac (16.5%) vaccines ($p < 0.05$). Similarly, the ChAdOx1 vaccine was associated with a greater number of symptoms compared to CoronaVac ($p < 0.05$) (Figure S1).

Regarding headaches, the ChAdOx1 (22.7%) vaccine reached a higher number of cases than the BNT162 (10.5%) and CoronaVac (3.5%) vaccines ($p < 0.05$).

For muscle pain, a higher prevalence was observed in the subjects vaccinated with ChAdOx1 (30.9%) compared to the groups receiving BNT162 (11.4%) and CoronaVac (5.9%) ($p < 0.001$). However, no significant differences were observed between the latter two groups regarding this symptom ($p = 0.22$) (Figure S1).

Regarding fatigue, differences were only observed between the BNT162 (16.3%) and CoronaVac (5.9%) vaccines ($p < 0.05$), indicating that BNT162 triggered this symptom more frequently. In subjects who reported fever, a higher frequency was observed with the ChAdOx1 (25.8%) vaccine compared to BNT162 (8.1%) and CoronaVac (2.3%) ($p < 0.001$).

A higher prevalence of chills was evidenced in the ChAdOx1 vaccine (12.4%) compared to the BNT162 (3.2%) and CoronaVac vaccines ($p < 0.01$). However, when comparing CoronaVac and BNT162, no significant differences were identified in the averages of subjects with this adverse effect ($p = 0.09$).

In terms of nausea, the subjects who received the ChAdOx1 (11.3%) vaccine exhibited a higher incidence compared to those vaccinated with BNT162 (1.6%) and CoronaVac ($p < 0.01$).

Additionally, a more pronounced prevalence of flu-like adverse effects was noted when comparing the ChAdOx1 (9.3%) and CoronaVac (2.3%) ($p < 0.05$) vaccines. Nevertheless, no significant disparities were evident between BNT162 and ChAdOx1 ($p = 0.06$) or between BNT162 and CoronaVac ($p = 0.38$) (Figure S1). Moreover, there were no detectable differences among subjects who received the three vaccines in terms of lymph node enlargement. Table 2 summarizes the frequency of adverse effects reported for each vaccine.

Table 2. Adverse effects reported by subjects after first shot of BNT162, CoronaVac, and ChAdOx1 vaccines.

Adverse Effect	BNT162	ChAdOx1	CoronaVac
Local pain	61 (49.6%)	31 (31.9%)	14 (16.5%)
Headache	13 (10.5%)	22 (22.7%)	3 (3.5%)
Muscle pain	14 (11.4%)	30 (30.9%)	5 (5.9%)
Fatigue	20 (16.3%)	13 (13.4%)	5 (5.9%)
Fever	10 (8.1%)	25 (25.8%)	2 (2.3%)

Chill	4 (3.2%)	12 (12.4%)	0 (0%)
Lymph node enlargement	1 (0.8%)	1 (1%)	0 (0%)
Nausea	2 (1.6%)	11 (11.3%)	0 (0%)
Flu-like symptoms	4 (3.2%)	9 (9.3%)	2 (2.3%)

3.3. Adverse Effects of the COVID-19 Vaccines in Atopic and Non-Atopic Subjects

After analyzing the differences in adverse effects of the different vaccines, our investigation focused on the presence of significant differences between atopic and non-atopic individuals based on the first shot data. When considering all vaccines, we found no significant differences between the atopic and non-atopic groups for any of the adverse effects reported (Table S1). We also conducted an analysis based on the type of vaccine administered and reclassified individuals into atopic and non-atopic groups to assess whether there was a statistically significant difference in the presence of adverse effects for the same vaccine (Figure 3, Tables S2–S4). When analyzing local pain, headache, fatigue, nausea, and flu-like symptoms, no statistical differences were observed between the atopic and non-atopic groups, although there was a tendency ($p = 0.053$) for a greater adverse effect of headaches in atopic individuals immunized with ChAdOx1 when compared to non-atopic individuals (Figure 3, Table S3).

When analyzing muscle pain, fever, and chills as a result of the ChAdOx1 vaccine, these symptoms were more common in atopic individuals than in non-atopic individuals ($p < 0.05$). In contrast, when the BNT162 vaccine was studied, non-atopic individuals were found to have fever more frequently than atopic individuals ($p < 0.05$) (Figure 3, Table S2).

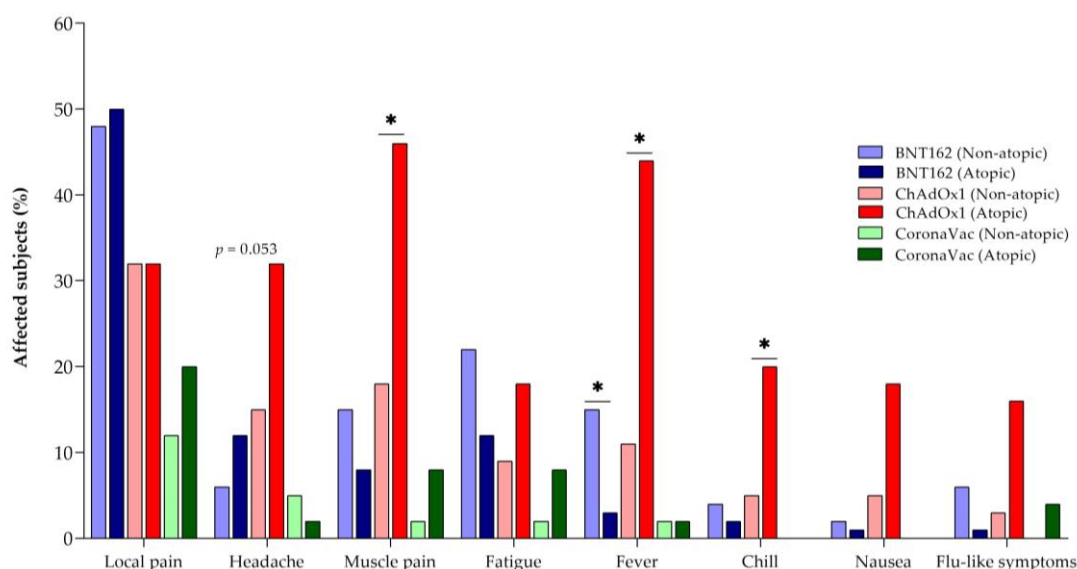


Figure 3. Main adverse events associated with the administration of the first dose of the BNT162, CoronaVac, and ChAdOx1 vaccines in the non-atopic and atopic groups. The colors indicate the type of vaccine, and the intensity of the relative color indicates the non-atopic (lighter) or atopic (darker) groups. * $p < 0.05$.

4. Discussion

The present study aimed to investigate the adverse effects of three COVID-19 vaccines (ChAdOx1, BNT162, and CoronaVac) in individuals with or without atopy, focused on respiratory allergies (allergic rhinitis and/or asthma). We assessed self-reported participant information to elucidate the common adverse effects and administered questionnaires (RCAT and ACT) to investigate allergic symptoms; in addition, we performed SPT and *D. farinae*-specific IgE quantification, which is one of the most important allergen sources that causes respiratory allergic diseases in tropical and sub-tropical regions. All atopic individuals were positive in the SPT and/or for specific IgE, and non-atopic individuals were negative for both tests. The total IgE level was not assessed in this study because in countries where there are a large number of cases of helminth parasitosis, such as Brazil, total IgE results may not be truly representative due to influence of *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Toxocara* spp. Allergens [32].

The results demonstrated that most subjects, regardless of being atopic, showed no adverse effects after the first and third doses, independent of the vaccine applied. When we evaluated the vaccinations separately, ChAdOx1 and BNT162 revealed a similar number of adverse effects after the first shot compared to CoronaVac. The study did not analyze the data from the third shot because during the collection period, the number of participants complying with the second shot was smaller. Thus, we used the data from the first shot for the examination of the side effects typically reported following immunization. In general, individuals who received a first shot of the ChAdOx1 vaccine exhibited more side effects, such as headache, muscle pain, fever, chills, nausea, and flu-like symptoms, compared to those who received the BNT162 vaccine. Local pain, fever, fatigue, and myalgia, although causing discomfort, are commonly observed following vaccinations and are typically not concerning [33]. A cross-sectional study analyzed the self-reported side effects of the BNT162 vaccine, with similar results; the subjects mostly reported headaches, chills, fatigue, and fever as systemic symptoms [34]. In another cross-sectional study conducted with healthcare professionals, with an average age of 31 years and who were vaccinated with ChAdOx1, a higher frequency of side effects was also observed after the first shot. The predominant symptoms included headache, fatigue, fever, muscle pain, chills, and nausea, along with other symptoms like joint pain, loss of taste, and loss of appetite [35]. In our study, the most commonly reported side effect in both ChAdOx1 and BNT162 vaccine groups was local pain. In addition, the participants did not report any allergic symptoms or anaphylaxis that could be linked to the vaccines. In other studies, including phase II clinical trials, more than 80% of the participants also reported the same effect after vaccination [36,37].

To investigate whether individuals with atopic conditions such as allergic rhinitis and/or asthma experience more prominent side effects than non-atopic individuals after vaccination and given that individuals who received the ChAdOx1 vaccine showed significantly more adverse effects compared to those who received BNT162 and CoronaVac, we stratified the effects by group and vaccine administered. Atopic individuals who received ChAdOx1 reported the most adverse effects such as muscle pain, fever, and chills compared to non-atopic individuals. However, in another study evaluating the BNT162 vaccine, it was observed that many individuals who self-reported allergies after vaccination experienced side effects such as vomiting, headache, gastrointestinal disturbances, and cardiac palpitations compared to non-allergic individuals [19]. Interestingly, in our study, non-atopic individuals mostly reported headaches when compared to atopic individuals in the BNT162 group. In another study evaluating the effect of COVID-19 vaccination on severe asthma, less than 20% of asthmatic patients reported experiencing the common adverse effects such as local pain, weakness, headache, myalgia, arthralgia, and fever after receiving an mRNA vaccine [38]. A different study assessed the side effects after vaccination with BNT162 and CoronaVac in individuals with allergic diseases and observed a predominance of local pain among the adverse effects [39]. The authors reported that local adverse effects such as swelling and redness were noted in allergic patients after receiving the BNT162 vaccine, and these effects tended to be more persistent than in non-allergic individuals [19]. Regarding the CoronaVac vaccine, in one study, no adverse effects were observed in atopic individuals; this was also observed in allergic individuals with respiratory allergies, demonstrating that the vaccine with inactivated virus has less impact on post-vaccine symptoms [40]. Although our study was focused on adverse effects, future studies should be conducted to assess IgG antibodies against SARS-CoV-2 in both atopic and non-atopic groups to improve the knowledge on vaccine efficacy and elucidate any potential differences in immunogenicity.

The non-atopic group comprises patients with negative SPT and/or specific-IgE ELISA results. However, it is noteworthy that some patients with asthma and rhinitis were also included in non-atopic group. This inclusion may initially appear contradictory as they are often associated with allergic sensitization. However, in our cohort, these patients exhibited negative SPT and serology tests outcomes, suggesting the possibility of non-IgE-mediated mechanisms underlying their respiratory symptoms. Non-IgE-mediated mechanisms, such as irritant triggers, proteases, or non-specific airway hyper-responsiveness, could contribute to the asthma and rhinitis symptoms in these individuals. Therefore, while they presented clinical manifestations of allergy, their negative SPT and specific-IgE results indicate a non-atopic endotype. On the other hand, all the individuals from the atopic group had respiratory allergies, but none of them reported severe allergic reactions or anaphylaxis that could be attributed to the vaccines, in contrast to the findings from other studies [17,18]. This observation is

remarkable and suggests that despite their atopic status, these individuals did not exhibit a higher propensity for vaccine-related adverse events. These results emphasize the importance of assessing specific IgE levels to understand the underlying mechanisms contributing to vaccine reactions in atopic individuals.

Although allergy is the most prevalent immune disorder, affecting millions of people worldwide, the EACCI (European Academy of Allergy and Clinical Immunology) declared that the COVID-19 vaccine can be administered to allergic patients, except for individuals with allergy to the vaccine components. For BNT162, polyethylene glycol (PEG) is the most hyper-reactive component and ethylenediaminetetraacetic acid (EDTA) is the most allergenic compound found in the ChAdOx1 vaccine [41–43]. Our study was focused on investigating the role of respiratory atopy in the adverse effects related to the vaccines. Further studies should be conducted to determine the details of the vaccine pharmacodynamics and other relevant characteristics that could potentially influence the occurrence of adverse effects. This would provide a more comprehensive understanding of the observed adverse effects and their potential associations with specific vaccine formulations.

The total absence of reported allergic or anaphylactic reactions among the 305 individuals, despite a substantial portion of the cohort being comprised of individuals with asthma and rhinitis, highlights the safety of COVID-19 vaccination in this population.

5. Conclusions

Overall, our study contributes valuable evidence supporting the safety of COVID-19 vaccination in individuals with respiratory allergies. However, the higher incidence of mild adverse events after receiving the ChAdOx1 vaccine in atopic individuals highlights the necessity of providing guidance on potential adverse effects when administering some categories of COVID-19 vaccines. Healthcare providers should carefully weigh the potential benefits and risks of each vaccine in the context of the medical history and allergy profile of their patients to optimize vaccine safety and effectiveness.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1. Figure S1: Comparison among BNT162, ChAdOx1, and CoronaVac COVID-19 vaccines regarding absence or presence of adverse effects reported by subjects; Table S1. Main adverse effects reported by atopic (n = 166) and non-atopic subjects (n = 139) in the first shot of BNT162, ChAdOx1, and CoronaVac vaccines; Table S2. Main adverse effects reported by atopic (n = 78) and non-atopic subjects (n = 45) in the first shot of BNT162 vaccine; Table S3. Main adverse effects reported by atopic (n = 44) and non-atopic subjects (n = 53) in the first shot of ChAdOx1 vaccine; Table S4. Main adverse effects reported by atopic (n = 45) and non-atopic subjects (n = 40) in the first shot of CoronaVac vaccine.

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Informed Consent Statement: Informed consent was obtained from all subjects.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors upon request.

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2. Correlato de imunidade induzidos por vacinas específicas e sua eficácia na proteção contra COVID-19

*Manuscrito a ser submetido para publicação no Periódico “**Expert Review of Molecular Diagnostics**”, da editora Taylor & Francis (Fator de Impacto: 5.1), com previsão de submissão em julho de 2024.*

2.1. Carta de apresentação: *Expert Review of Molecular Diagnostics*

Cover letter

Prof. Attila T Lorincz

Editor-in-Chief, *Expert Review of Molecular Diagnostics*, Taylor & Francis

Queen Mary University of London

Mile End Road, London, United Kingdom, E1 4NS

Dear Prof. Attila T Lorincz,

I am submitting the article entitled “**Prevalence of SARS-CoV-2 neutralizing antibodies in individuals vaccinated and unvaccinated for COVID-19 in Brazil using point-of-care diagnostic test**” for your consideration in form of Original Research, with authorship of Laura Alves Ribeiro Oliveira, Camila Amormino Corsini, Alessandro Sousa Correa, Marielle Máximo Barbosa, Rafaella Fortini Grenfell e Queiroz, Miguel Junior Sordi Bortolini, Rafael de Oliveira Resende Ernesto Akio Taketomi, for publication in *Expert Review of Molecular Diagnostics*.

This work investigates the use of a point-of-care platform for detection of neutralizing antibodies (NAbs) in three groups of individuals: vaccinated against COVID-19, convalescent and unvaccinated without SARS-CoV-2 infection (naïve). Most subjects were vaccinated with Pfizer BioNTech mRNA vaccine. The highest levels of NAbs and anti-S IgG were found in individuals vaccinated following convalescent and naïve. There was correlation between these two variables in both groups. These findings demonstrate that POC was able to detect the levels of NAbs with distinctive profiles in groups of vaccinated individuals and those not vaccinated with or without previous history of infection by SARS-CoV-2, highlighting the importance of using these platforms in the stratification of risk groups for public health concerns.

It is our acknowledgement that this article is original, and it has not been published in any other scientific journal. The study was conducted in compliance with ethical research standards for humans.

We consider that this manuscript finds the journals’ scope once it reports a diagnostic test that is used in places of care with limited resources, such as in developing countries, in the case of Brazil. Our results will provide relevant information that elucidated the importance of point-of-care tests in assessing the immunological response in infections or post-vaccination in the COVID-19 environment.

All authors have given their approval to the content presented and submitted manuscript to the Journal of Sports Science. Conflicts of interest have not been disclosed by the authors.

We appreciate your attention and anticipate your feedback.

Sincerely,

Ernesto Taketomi, MD, PhD

Laboratory of Allergy and Clinical Immunology

Institute of Biomedical Sciences

Federal University of Uberlândia

Uberlândia, Brazil

2.2. Manuscrito

Prevalence of SARS-CoV-2 neutralizing antibodies in individuals vaccinated and unvaccinated for COVID-19 in Brazil using point-of-care diagnostic test

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Abstract: Since the onset of the pandemic, diagnostic tests have played a crucial role in identifying and mitigating the spread of the SARS-CoV-2 virus. Point-of-care (POC) tests have emerged as a prominent tool in combating the COVID-19 pandemic, including the detection of neutralizing antibodies (NAbs). The aim of this study was to evaluate the prevalence of neutralizing antibodies (NAbs) using a POC test in individuals vaccinated with mRNA, viral vector or inactivated virus-based vaccine, as well as in unvaccinated ones, with or without history of SARS-CoV-2 infection. Blood samples were collected from 140 COVID-19 vaccinated (V), 122 unvaccinated convalescent (UC), and 48 unvaccinated naïve (UN) adult volunteers. NAbs were assessed using a lateral flow immunochromatography assay (LFIA) and compared to anti-S (Spike) IgG levels, determined by ELISA. The majority participants received the BNT162 vaccine (44.4%), followed by CoronaVac (32.6%) and ChAdOx1 (20.8%). Detectable NAbs were observed in 137 (97.0%) of the V group, followed by 81 (66.4%) of convalescent (UC), and 1 (2.08%) of naïve (UN) individuals. The percentage of NAbs was notably higher in V (mean=86.7%) compared to the UC (mean=42.1%) and UN (mean=1.9%) groups. Anti-S IgG levels were also significantly higher in V (RI=2.2±0.4) compared to UC (RI=1.5±1.0) and UN (RI=0.4±0.3) individuals. Furthermore, a moderate correlation was observed between NAbs and anti-S IgG levels among vaccinated (r=0.448) and

non-vaccinated/convalescent ($r=0.550$) individuals. The results from the POC test proved to be effective in assessing prevalence of NABs in both vaccinated individuals and those unvaccinated, with or without a previous history of COVID-19.

Keywords: immunochromatography, neutralizing antibodies, COVID-19, SARS-CoV-2, spike

1. Introduction

COVID-19, a disease caused by the SARS-CoV-2 and characterized by severe acute respiratory syndrome, precipitated a global pandemic in 2020, whose social, cultural, and epidemiological effects persist. For months, Brazil has been at the forefront of the pandemic, marked by a surge in cases and the emergence of novel variants, exacerbating the public health crisis. The Brazilian population has endured severe waves of infection, overwhelming its healthcare systems, and contributing to a substantial mortality rate. Additionally, the delay in implementing a COVID-19 vaccination program and the challenges in establishing an efficient diagnostic protocol and social isolation measures to control viral transmission have facilitated the rapid spread of SARS-CoV-2 throughout the country, with a far-reaching consequence globally. This is exemplified by the emergence of the Gamma (P.1) variant, one of the four viral strains primarily derived from the wild type, in the metropolitan area of Manaus, situated in the heart of the Amazon rainforest. This variant has been linked to increased transmissibility and possess a high potential for immune evasion due to evolutionary pressures. The core of this viral resistance lies in the accumulation of mutations in the viral spike (S) protein, particularly in the receptor-binding domain (RBD) region, which hinders antibody recognition and consequently impairing the efficacy of the immune response against the virus (1-3).

Since the onset of the pandemic, in association to social isolation measures and the utilization of other physical barriers, the urgent need to develop an effective vaccine to control the dissemination of the virus has spurred numerous teams in the technology field to implement a variety of cutting-edge platforms in establishing a novel cohort of vaccines. These include mRNA-based and viral vector-based vaccines, alongside other conventional platforms such as inactivated virus (4-6). In a unprecedented move, regulatory agencies immediately approved the use of these vaccines aiming to mitigate the devastating effects of the SARS-CoV-2 worldwide. Consequently, several studies have been conducted to understand how the mass immunization could establish a collective barrier against the virus, based on the biochemical composition and protective effect of each vaccine (4-6). Even as global vaccination programs have started, the real-world studies have proven to be crucial to understand the immunological mechanisms

driven by these vaccines.

The primary objective of COVID-19 vaccines is to induce a memory immune response against the virus. This protective effect involves a complex interaction of innate and adaptive components, such as CD4⁺ and CD8⁺ T cells, natural killer (NK) cells, macrophages, and memory B cells, modulated by cytokines and chemokines. Additionally, these vaccines elicit a humoral immune response by stimulating the production of antibodies, particularly IgG subclasses and IgA, which are involved in several immunological processes aimed at eliminating the virus, including Fc-mediated effector functions and neutralization (7, 8).

Understanding the dynamics of neutralizing antibodies (NAb) is essential for monitoring humoral immune protection, particularly in the context of emerging variants. The principle of neutralization is based on the potential capacity of the antibody of targeting viral S protein, thereby blocking its interaction with the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of host cells and preventing viral entry. Additionally, NAb can trigger immune responses that lead to the destruction of virus-infected cells, further limiting viral replication and spread within the body. Some studies indicate that mutations found in the S protein have led to increased viral escape from these antibodies, significantly raising the potential for the emergence of additional variants and disease outbreaks, even among the vaccinated population (9, 10).

The monitoring of NAb against SARS-CoV-2 has been used in several studies involving uninfected (naïve), convalescent, and vaccinated individuals for assessing the effective activation of humoral immune response on protection against infection and reduction in the severity of the disease (11, 12). The prevalence of NAb in vaccinated individuals has been associated with immunity correlates, the levels of which are correlated to anti-S IgG (13). However, while these antibodies play a crucial role in collective protection, the first generation of vaccines designed for wild-type virus elicits a weaker immune response against new variants, including Omicron and its subvariants, highlighting the necessity for the development of new generations of vaccines with greater efficacy against the different viral lineages (14).

The immune response following natural infection also tends to be broad and includes the generation of high-affinity NAb, in contrast to naïve individuals, who lack pre-existing NAb against SARS-CoV-2, rendering them susceptible to infection. In addition, naïve individuals exhibit very low levels of NAb after booster vaccination, compared to previously infected individuals (14). Notably, convalescent individuals may show higher levels of these antibodies even before vaccination, likely modulated by IL-6 and cTfh cells produced and activated during infection (15).

During the pandemic, diagnostic tests played a crucial role in identifying and controlling the spread of the SARS-CoV-2 virus. The emergency status also highlighted the widespread use of point-of-care (POC) tests, primarily due to their cost-effectiveness (16). These diagnostic tests are designed to be used at or near the site of patient care, such as clinics, pharmacies, or even at home, without the requirement for specialized laboratory equipment. The main advantages of POC diagnostics include their speed, ease of use, and the ability to deliver results within minutes to hours, which is crucial for timely clinical and public health decision-making (17). Particularly in the early stages of the pandemic, the detection of anti-SARS-CoV-2 antibodies was important on monitoring the status of immunity and lateral flow immunoassay (LFIA) have been prominent as POC test for assessing Nabs, serving as a reliable and simple tool for determining vaccine efficacy (18).

The method is based on immunochromatography, in which immune components are combined to aid the migration of the analyte along the nitrocellulose membrane using capillary force (19). In the context of COVID-19, although the test provides rapid results without the need for robust laboratory equipment, the performance in detection may be relative, as low levels of these antibodies are observed in the early stages of infection. Nonetheless, the test has provided reliable results in measuring post-vaccination antibodies, including Nabs (20-23). Investigating the prevalence of these antibodies in COVID-19 using POC tests is of outstanding importance for public health surveillance. This evaluation helps assess the impact of previous infection waves and vaccination efforts, providing essential data for forecasting future trends and preparing for potential resurgence of the virus.

Therefore, in this study, we aimed to determine the prevalence of SARS-CoV-2-specific NAbs in individuals vaccinated with viral vector, mRNA, or inactivated-based virus vaccines, as well as unvaccinated ones with or without recent infection, using LFIA platform. Investigating this immune profile in COVID-19 using rapid tests is of outstanding importance for public health surveillance, particularly in Brazil, which was a major epicenter of the pandemic. Such investigations may contribute to more effective control and mitigation strategies.

2. Materials and methods

2.1. Study design and sample collection

This observational study involved both qualitative and quantitative diagnostic methods with 310 volunteers from Minas Gerais, southeast region of Brazil, aged between 18 and 50 years old. The groups and number of individuals are reported in Figure 1. The study received approval from the Ethics Committee for Human Research at the Federal University of Uberlândia (protocol CAAE50001421.7.0000.5152), Oswaldo Cruz Foundation (protocol CAAE50001421.7.3003.5248), and the National Research Ethics Council (protocol CONEP30428720.3.0000.5091). All participants provided informed consent and age/sex/type of vaccine data were collected in a case report form.

A total of 140 individuals vaccinated for COVID-19 with BNT162, CoronaVac, or ChAdOx1 vaccines (vaccinated, V) were recruited at the Federal University Hospital, Uberlândia, from June 2021 to June 2022, by presenting an updated vaccination card indicating the history of COVID-19 vaccines. The Brazilian Vaccination Program for COVID-19 started in January 2021, initially focusing on a two-dose schedule. The monovalent BNT162b2 and ChAdOx1 vaccines were administered with an 8-week interval between the first and second doses, while the CoronaVac vaccine followed a 28-day interval. A booster dose (dose 3) was included 4 months after second dose.

Unvaccinated patients with suspected or confirmed diagnosis of SARS-CoV-2 were attended at the Baleia Hospital, Belo Horizonte from May 2020 to May 2021 and invited to join the study over a 6-month period for clinical evaluation. They had nasopharyngeal swab collected and the samples were sent to a core facility (Ezequiel Dias Foundation, Funed, Belo Horizonte) for RT-PCR and results were accessed by electronic medical records. They were grouped according to RT-PCR results for SARS-CoV-2, in which 122 individuals had moderate to severe symptoms and positive RT-PCR (unvaccinated/convalescent, UC) and 48 unvaccinated patients had negative RT-PCR (unvaccinated/naïve, UN).

Blood samples were collected from all individuals for analysis of NAbS and spike-specific antibodies (anti-S) IgG. For UC and UN, blood was collected 15 days after the onset of symptoms. Samples were centrifuged at 3,000 x g for 5 minutes, and sera were stored at -20°C.

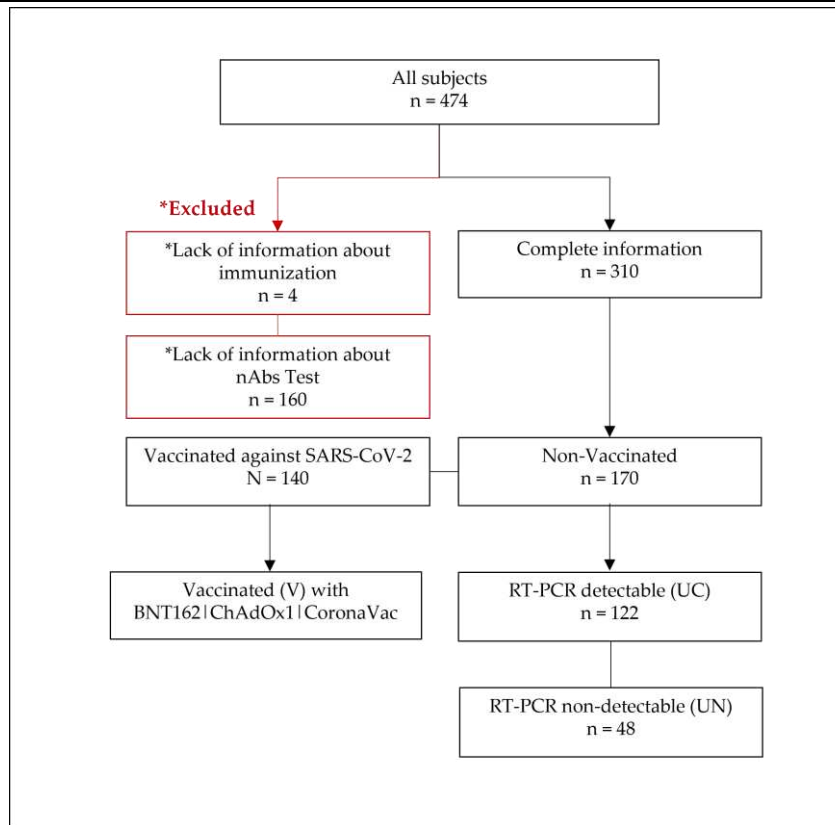


Figure 1. Study design.

2.2. Detection of NAbs by LFIA

The fluorescence-based LFIA (ECO Diagnóstica, Nova Lima, Brazil) for detection of NAbs against SARS-CoV-2 beta (B.1.351) and gamma (P.1) strains was conducted in all groups: vaccinated (V), unvaccinated/convalescent (UC) and unvaccinated/naïve (UN) following the manufacturer's guidelines. The serum samples (100 µL) and extraction buffer (200 µL) were added to a microtube, followed by lyophilized beads with RBD/europium and ACE-2/biotin recombinant proteins, incubated at 37°C for 20 minutes. Afterwards, 100 µL of each mixture was added to the test cassette, followed by an additional 15-minute incubation at room temperature and results were displayed. Fluorescence intensity was read using provided reader (F200 Fluorimeter, ECO Diagnóstica) and inhibition index above 20% indicated the presence of NAbs.

2.3. Spike-specific (anti-S) IgG antibody

Anti-S IgG was assessed by ELISA in all groups. Briefly, 96-well plates (Corning, Glendale, AZ, USA) were sensitized with 200 ng/well of recombinant S protein in 50 µL/well phosphate-buffered saline (PBS), pH 7, for 16h at 4°C. Subsequently, the plates were washed five times with PBS and blocked with 2% skimmed milk in PBS (blocking buffer) for 1.5h at room temperature. The plates were washed, and sera were diluted at 1:40 in 1% blocking buffer

and added (50µL/well), followed by 2h incubation at room temperature. After another round of washing, the plates underwent a 90-minute incubation with anti-human IgG/HRP (Sigma-Aldrich, San Louis, MO, USA) diluted in PBS (1:60,000). After additional washing, the reaction was initiated by adding 3,3',5,5'-tetramethylbenzidine (TMB) (Sigma-Aldrich) for 10 minutes and stopped with 1N H₂SO₄. Optical density (OD) was read at 450 nm using the Multiskan FC plate reader (ThermoFisher, Waltham, MA, USA). Reactivity index (RI) was determined by relative OD (sample OD – blank OD)/calibrated OD (0.1508). A positive threshold was considered as 1.

2.4. Statistical analyses

The ROC curve was performed using MedCalc 22.018 (MedCalc Software, Ostend, Belgium). Other statistical analyses and graphs were generated by GraphPad Prism 8.0.1 (GraphPad, Boston, MA, USA). Statistical differences in anti-S IgG and NAbs levels among V, UC, UN were analyzed using the Kruskal-Wallis test. Differences between number of individuals with absence/presence of NAbs per group and differences among number of vaccinated individuals per vaccine type were assessed by Chi-square test. Fisher's exact test was used to evaluate differences between nominal variables. The correlation coefficient between anti-S IgG and NAbs was calculated using the non-parametric Spearman correlation test. All tests were two-tailed, considering $p < 0.05$ as statistically significant.

3. Results

3.1. Demographic data and vaccination scheme

Statistical differences were noted between women and men in both the UC and UN groups concerning participant demographics ($p < 0.001$; $\chi^2 = 9.7$). Additionally, there was a significant statistical contrast between the genders in the V and UC groups ($p < 0.0001$; $\chi^2 = 12.3$). However, there was no statistical difference between male and female in the V and UN groups ($p = 0.5457$; $\chi^2 = 0.36$). The age values were different among all groups ($p < 0.0001$). In V group, the interval between vaccination and blood collection, concomitant to survey inclusion, was 8.1 ± 2.6 months.

Vaccinated individuals who completed the first vaccination schedule (2 doses) were preferably immunized with the BNT162 vaccine (44.4%), followed by CoronaVac (32.6%) and ChAdOx1 (20.8%). For the booster dose, the majority were immunized with the BNT162 (43.7%) while remained took ChAdOx1 (31.2%). CoronaVac was not included in the booster dose, and those who took this vaccine should receive BNT162 and ChAdOx1, increasing the proportion among them ($p < 0.0001$; $\chi^2 = 50.7$).

Table 1. Demographic characteristics and COVID-19 vaccine distribution.

Characteristics	Vaccinated (V)			Unvaccinated	
				Convalescent (UC)	Naïve (UN)
Participants (n)	140			122	48
Gender					
Male	54 (38.5%)			73 (59.8%)	16 (33.3%)
Female	88 (62.8%)			49 (40.1%)	32 (66.6%)
Age					
Median	26.6			59	58
Vaccines	BNT162	CoronaVac	ChAdOx1		
dose 1	64 (45.7%)	47 (33.5%)	30 (21.4%)	-	-
dose 2	64 (45.7%)	47 (33.5%)	30 (21.4%)	-	-
dose 3	63 (45%)	-	45 (32.1%)	-	-

3.2. Detection of NAbs

Detectable NAbs against SARS-CoV-2 beta (B.1.351) and gamma (P.1) strains, assessed by LFIA, were observed in 137 (97.0%) vaccinated individuals (V), regardless of the type of vaccine (Figure 2). This was followed by 81 (66.4%) convalescent individuals (UC), and 1 (2.08%) naïve (UN). NAbs could not be found in only 3 (2.14%) individuals on group V, 41 (33.6%) in UC, and 47 (97.9%) in UN. The percentage of NAbs was higher in V (mean=86.7%), followed by UC (mean=42.1%), and lower in UN (mean=1.9%), $p<0.0001$.

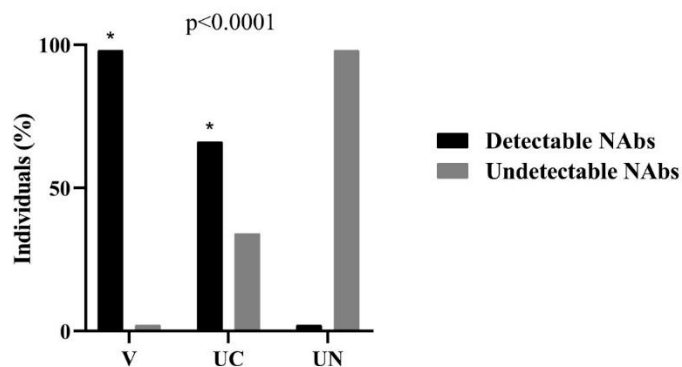


Figure 2. Number of individuals with detectable and undetectable NAbs in vaccinated (V), unvaccinated/convalescents (UC) and unvaccinated/naïve (UN) groups. * $p<0.0001$.

3.3. Anti-S IgG levels and correlation with NAbs

Anti-S IgG levels is a strong indicative of immune correlates of protection against SARS-CoV-2 since humoral immune response plays an important role on virus neutralization and Fc-

mediated functions. Notably, vaccinated individuals (V) reached higher mean anti-S IgG levels ($RI=2.2\pm0.4$), compared to UC and UN ($RI=1.5\pm1.0$ and $RI=0.4\pm0.3$, respectively; $p<0.0001$) (Figure 3). However, although vaccinated individuals are expected to have positive anti-S IgG levels, 3 (2.1%) individuals had IgG levels below cut-off in group V and 29 (23.7%) individuals were negative in group UC. On the other hand, 3 (6.2%) of unvaccinated individuals without COVID-19 (UN) had positive IgG.

The correlation between the NAbs and the levels of anti-S IgG is illustrated in Figure 4. A moderately positive correlation was observed among them in V group ($r=0.448$; $p<0.0001$) as well as UC group ($r=0.550$; $p<0.0001$). However, no correlation was found in UN group ($r=0.177$; ns).

LFIA showed a remarkable diagnostic capacity compared to ELISA-IgG, as evidenced by an area under the curve (AUC) of 0.937 with high sensitivity (88.51%), specificity (92.11%) and association criterion > 20 (Figure 5).

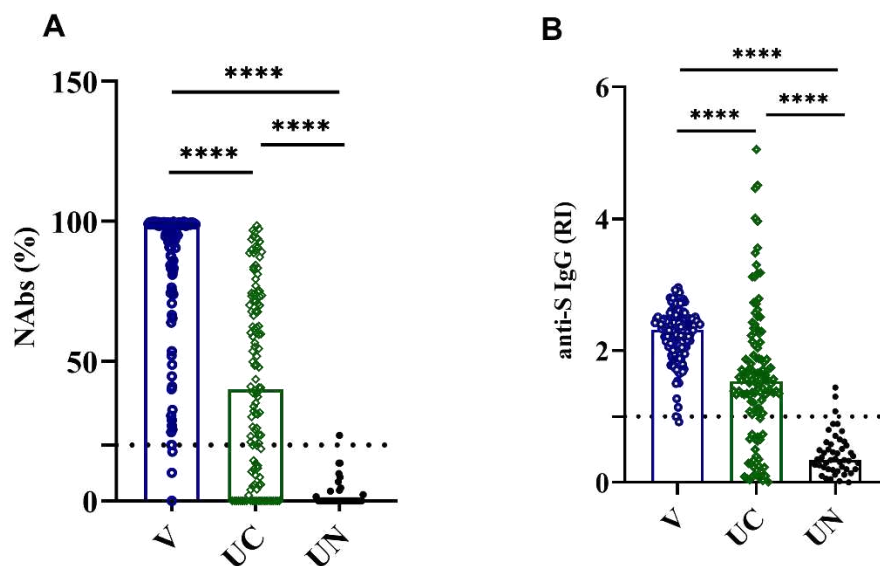


Figure 3. Levels of NAbs (A) and Spike-specific (anti-S) IgG (B) in vaccinated (V), unvaccinated/convalescent (UC) and unvaccinated/naïve (UN). Differences among the groups were compared using One-Way ANOVA followed by Kruskal-Wallis's test. The reactivity index (RI) of IgG anti-Spike protein in both groups is shown (Cutoff = 1), with the range for detectable NAbs indicated by dashed lines ($< 20\%$). Significant considered $p < 0.05$ the data used median.

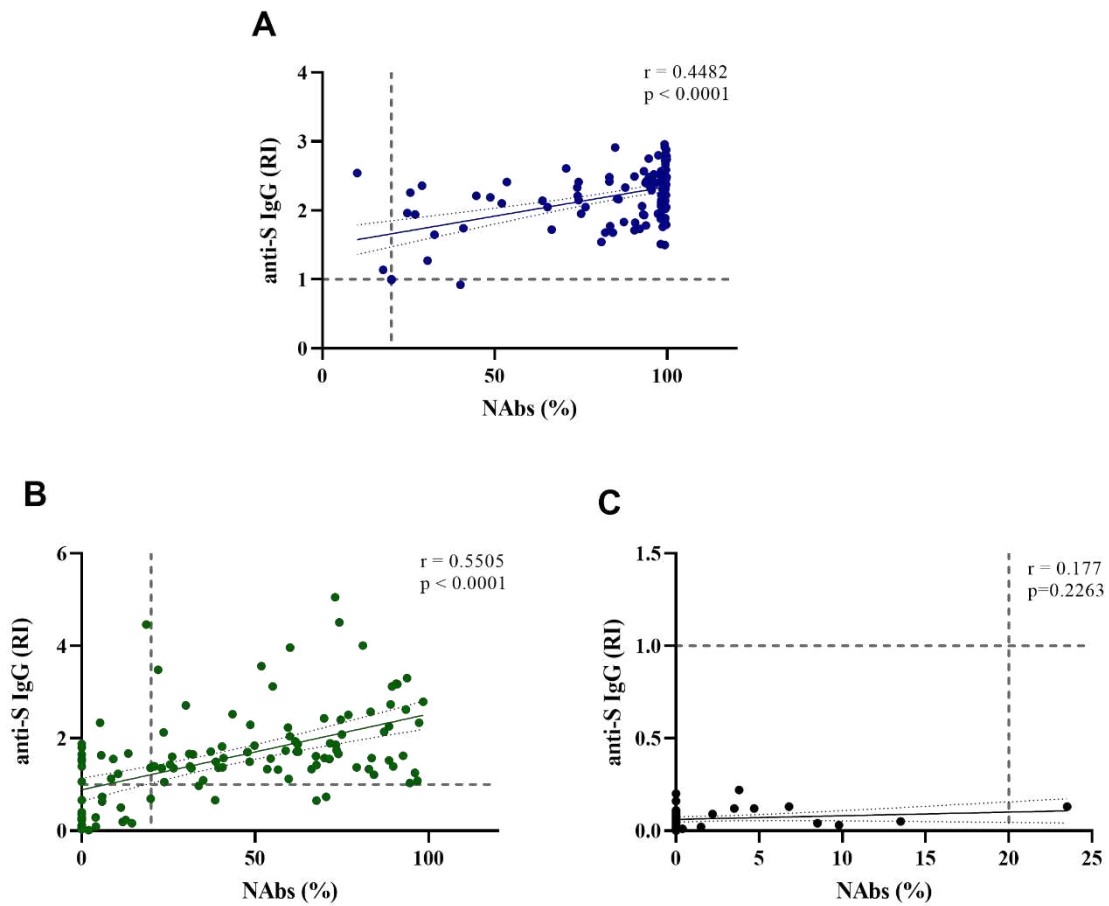


Figure 4. Correlation coefficients (r) between levels of NAbs and IgG anti-spike in the groups (A) vaccinated, V, (B) unvaccinated/convalescent, and (C) unvaccinated/naïve, UN were calculated by Spearman's correlation coefficient test. Data are reported as percentage (%) for NAbs and as reactivity index (RI) for IgG anti-spike. The cutoffs to axis X (NAbs) and axis Y (IgG) are represented by the dashed lines in light gray, with the cutoff for axis X set at 20 and for axis Y set at 1.

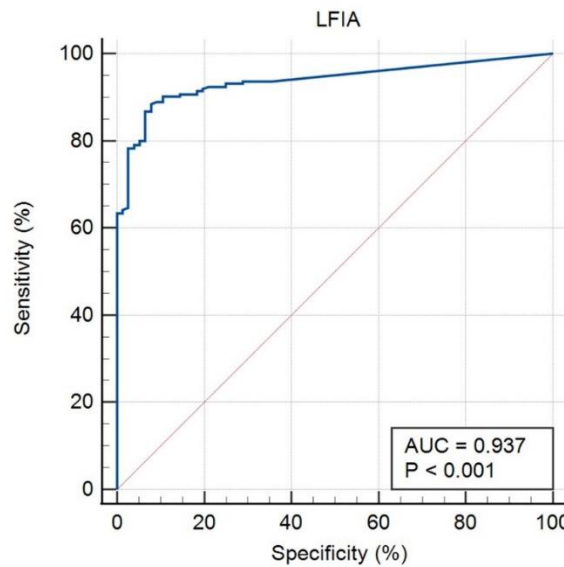


Figure 5. ROC curve illustrating the performance of the lateral flow immunochromatographic assay (LFIA) in comparison to anti-S IgG for the detection of neutralizing antibodies (NAbs) against SARS-CoV-2. The area under the curve (AUC) is 0.937, indicating high sensitivity (88.51%), specificity (92.11%) and an association criterion >20 . Statistical significance was determined as $p < 0.001$.

4. Discussion

The present study assessed the prevalence of neutralizing antibodies (Nabs) in vaccinated (V) individuals, as well as those vaccinated with (UC) or without (UN) previous infection by SARS-CoV-2, and compared this data to anti-S IgG levels, determined by ELISA. The presence of NAbs in individuals who received the vaccine and those who were infected was expected, given their close contact with the virus itself, and consequently with S protein. Furthermore, the choice of a reliable test to distinguish infected and non-infected individuals is crucial for understanding the dynamics of NAbs in these groups. In our study, we included individuals who were vaccinated, and those who presented symptoms underwent testing with the gold standard RT-PCR to confirm the infection. Thus, individuals were grouped according to their previous contact with the S protein, either through vaccination or infection. The levels of NAbs were notably higher in groups V and UC compared to UN, suggesting a heightened prevalence of these antibodies in individuals previously sensitized by either vaccination or infection. This finding highlights the importance of utilizing RT-PCR as an adjunctive diagnostic tool to discern between immune responses triggered by vaccination versus infection. RT-PCR stands as the gold standard test for identifying the presence of the virus in nasopharyngeal samples,

and its use is imperative during the acute phase of SARS-CoV-2 infection, coinciding with the viral incubation period, to ensure enhanced validation and confirmation of infection (24, 25).

LFIA tests fall under the category of point-of-care testing (POCT), a subtype of rapid diagnostic tests, and have been developed to enhance the screening and diagnosis of COVID-19 during pandemic period (26). Nevertheless, the performance of these tests is hindered by the occurrence of false negatives and false positives, primarily due to deficiencies in sample collection techniques and the underreporting of cases, as individuals often neglect to notify public health authorities of positive results (27, 28). In this regard, certain LFIA tests in Brazil have been validated for the quantification of NAb and have proven to be a valuable tool for assessing the efficacy of immunization and protection against various virus variants.

Studies have evaluated the humoral immune response of SARS-CoV-2 in convalescent individuals who recovered after infection, revealing increased IgG antibodies and the generation of virus-specific memory T cells, which confer protection against subsequent severe infection (29). However, only individuals with severe COVID-19 exhibited long-lasting immune memory compared to those with mild symptoms. These findings indicate that virus mutations contribute rapidly to immune evasion and modulation, heightening worries regarding reinfection with variants of concern (30). A total of 518 million doses of vaccines against SARS-CoV-2 have been administered in Brazil to date. Among the population, 88.5% have received at least one dose, while 82.2% have completed the entire vaccination regimen, either with two doses or a single dose. Additionally, 58.1% have received a booster dose. During the initial year of the vaccination program, over 377 million doses were administered. Among these, 53% received their initial dose, 93% completed the full vaccination schedule, and 40% received a booster dose (31-33).

Assessing the humoral immunity elicited by administered vaccines through rapid assays for the detection of antibodies specific to SARS-CoV-2 viral proteins could potentially aid in identifying individuals who would benefit from participation in vaccination campaigns aimed at preventing severe infections. However, it is crucial to note that the humoral immune response alone does not solely determine protection following COVID-19 vaccination or infection. This is attributed to the gradual decline in antibody levels over time post-vaccination. Therefore, cellular immunity assumes a prominent role in combating infection and enhancing vaccine efficacy, thereby bolstering the individual's overall immune response. This process is facilitated by the involvement of T CD8⁺ and T CD4⁺ cells, which specifically respond to viral particles and subsequently produce cytokines such as IFN- γ , IL-2, and TNF- α (34-36). The addition of adjuvants to vaccines can also elicit immune responses with different cell profiles. A study

conducted by Arunachalam et al. (2021) demonstrated that the adjuvant CpG1018-Alum induce a Th1 and Th2 profile reaction for the RBD and NP proteins of SARS-CoV-2, respectively (37, 38). Furthermore, it has been shown that physical activities play an important role as a natural adjuvant in boosting the immune response following vaccination, thereby increasing IgG levels (39).

The association between NAbs tests and specific IgG antibody levels for the S protein is being used as a predictive indicator to assess individual protective immunity, potentially substituting sophisticated neutralization tests (9). Thus, a positive correlation between NAbs assessed by LFIA and anti-S IgG measured by ELISA is observed in individuals from both the vaccinated and unvaccinated groups, provided that more than 15 days have elapsed since the onset of COVID-19 symptoms. Other studies have identified these antibodies as an essential biomarker for evaluating humoral response and the effectiveness of the COVID-19 vaccines post-immunization (10).

For investigating NAbs against SARS-CoV-2, the plaque reduction neutralization test (PRNT) is frequently employed to assess the cytopathic effect induced by the virus. While this method boasts high sensitivity and specificity, it necessitates the identification and live culture of novel coronaviruses and must be performed by qualified professionals in a Biosafety Level 3 laboratory. Nevertheless, practical limitations hinder its widespread utilization, prompting the development of numerous assays for the direct and indirect detection of NAbs against SARS-CoV-2 at lower Biosafety Level (11, 12). In our investigation, adopting a POCT for NAbs facilitates the assessment of the immune response and predicts the improvement of individuals during COVID-19 infection. Additionally, it can elucidate the efficacy of current vaccinations against SARS-CoV-2 in augmenting neutralizing antibodies, thereby bolstering humoral protection within the community. If warranted, this may advocate for the necessity of booster immunization to more effectively address the demands of diagnosis and treatment on a large scale within the realm of public health.

We observed that majority of vaccinated individuals and those who were unvaccinated but infected with SARS-CoV-2, as confirmed by RT-PCR positivity, exhibited similar levels of NAbs compared to the unvaccinated group, despite reported variations in these values in terms of duration and titer during vaccination in some studies. Conversely, in other trials, most participants showed increased levels above the detection threshold (21). Several studies have highlighted the challenge of detecting NAbs in the early stages of COVID-19 infection due to low detection levels, emphasizing the importance of developing immunochromatographic

techniques, such as LFIA, with increased sensitivity for improved dynamic monitoring of neutralizing antibodies in the vaccinated population against SARS-CoV-2 (22).

In our investigation of NAbs quantification, serum samples from individuals vaccinated with various immunobiological agents and those during SARS-CoV-2 infection (unvaccinated) with RT-PCT negative were employed. The commercial kit test successfully identified a high percentage of NAbs. Additionally, seroconversion of specific anti-S IgG was observed, displaying findings above the reactivity criteria. Similar outcomes have been reported in studies examining seroconversion among individuals inoculated with mRNA vaccines, with reported NAbs identified for up to 6 months following the second dosage of the vaccine. These findings are consistent with the results of the present research, as the majority of immunized individuals completed the initial immunization schedule (23, 40).

The study has limitations, including a lack of evaluating the immune response and comparison of age groups among individuals. Other studies examining children and adolescents vaccinated with CoronaVac revealed that the majority exhibited seroconversion, with increased levels of anti-S IgG and anti-N IgG observed after 6 months of vaccination with one or two full doses, suggesting that the vaccine was effective in conferring protection within this age group (41). The quantification of NAbs through rapid tests requires careful consideration due to the subjectivity of results. Some studies have observed a decline in NAbs levels in individuals during SARS-CoV-2 infection or vaccination, even when using the virus neutralization test (VNT) (42). Rapid assays, in certain studies, are considered unreliable in detecting "real" or "true" NAbs, as they pose technological and scientific challenges in their development and may only be capable of detecting binding antibodies, also known as total binding antibodies. This subject is currently under discussion and warrants further research, as NAbs serve as reliable indicators of protection in viral infections (43, 44).

We observed a limited association in levels of NAbs and anti-S IgG in the vaccinated group with different types of vaccinations. However, both tests displayed excellent predictive value through receiver operating characteristic (ROC) curve analysis, which was performed to identify the best cut-off indexes and validate the lateral flow immunoassay (LFIA) test for NAbs. The determined cut-off value exhibited higher sensitivity without compromising specificity, thereby confirming the effectiveness of the test. Therefore, ROC analysis validated the manufacturer's cut-off, demonstrating excellent sensitivity and specificity and indicating that the test is suitable for measuring NAbs against SARS-CoV-2 in either vaccinated or infected populations. Although this test showing this performance, as the does not reach 100%, it can result in a lower percentage of false negatives and false positives (45). For instance, in

situations with a high prevalence of the condition (illness), it may be desirable to employ increased thresholds for screening, while lower cut-offs could be helpful for diagnostic purposes (46, 47). A study revealed similarities with our results in the comparative approach between the LFIA test for detection of antibodies and the ELISA for anti-S IgG in infected and vaccinated patients, with a high correlation identified, particularly in the group that received only the ChAdOx1 vaccination (48).

5. Conclusion

Rapid assays have proven to be highly effective tools for evaluating humoral immunity and have significantly contributed to the surveillance of COVID-19 cases among infected individuals. Despite technical challenges and the complexities within the pandemic context, the LFIA, employed in this study to quantify antibodies, demonstrated effectiveness in identifying NAbs in individuals vaccinated with vaccines currently administered in Brazil. Investigating this immune profile in vaccinated individuals is essential for assessing vaccine efficacy, monitoring the duration of immunity, adapting to emerging variants, and optimizing public health strategies for future immunization programs.

Ethical Approval

The work was approved by CEP/UFU (Ethics Research Committee with Humans/Federal University of Uberlândia (Protocol CAAE-50001421.7.0000.5152) and Fiocruz/National Research Ethics Council (CONEP No. 30428720.3.0000.5091). All participants provided informed consent.

Authors' Contributions:

LARO, CAC, ASC, MJSB, RFGQ, ROR and EAT contributed to conceptualization, investigation, data collection, carried out data analyses and initially produced the design of the manuscript. All authors have read and approved the final submitted manuscript.

Disclosure statement

The authors did not report any potential conflicts of interest.

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Institutional Review Board Statement: The study was approved by CEP/UFU (Ethics Research Committee with Humans/Universidade Federal de Uberlândia (Protocol CAAE-50001421.7.0000.5152) and Oswaldo Cruz Foundation and the National Research Ethics Council (CONEP No. 30428720.3.0000.5091), all participants provided informed consent.

Data Availability Statement: The authors will provide the raw data that supports the conclusions of this article upon request.

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3. O papel da atividade física na resposta imune às vacinas contra COVID-19

Manuscrito a ser submetido no periódico “Journal of Sports Science” editora Taylor & Francis (Fator de Impacto: 3,4), com previsão da submissão em julho de 2024.

3.1 Carta de apresentação: *Journal of Sports Medicine*

Cover letter

Dr. Mark Williams

Editor-in-chief, *Journal of Sports Medicine*, Taylor & Francis

Florida Institute for Human & Machine Cognition

40 South Alcaniz Street, Pensacola, FL 32502, USA

Dear Dr. Mark Williams,

I am submitting the article titled “Adipokines and antibody response in individuals with physical activity and sedentary behavior following COVID-19 vaccination” for your consideration in form of Original Research with authorship of Laura Alves Ribeiro Oliveira, Letícia Cardoso Martins, Marielle Máximo Barbosa, Chamberttan Souza Desidério, Wesley Guimarães Bovi, Juliana Cristina Silva, Júlia Buiatte Tavares, Tássia Magnabosco Sisoneto, Guilherme Moraes Puga, Carlo José Freire de Oliveira, Virmondes Rodrigues Júnior, Miguel Junior Sordi Bortolini, Rafael de Oliveira Resende, and Ernesto Akio Taketomi, for publication in Journal of Sports Science.

This study demonstrates the role of lifestyle in modulating the immune response in individuals vaccinated with different platforms of vaccines against COVID-19 in male and female. The findings reveal low levels of leptin between active and sedentary individuals regardless of sex description. In women, higher levels of pro-inflammatory leptin and resistin adipokines were found, compared to men, however the levels of anti-S IgG were higher in women, also demonstrating higher levels of anti-inflammatory adiponectin cytokine, independent of lifestyle. These findings elucidate that although women have an inflammatory response profile, these responses do not interfere with vaccine protection in this group, demonstrating the protective effect of these molecules in post-vaccination for COVID-19, with a valuable impact for public health.

We confirm that the article is original and has not been published in any other scientific journal. It was conducted in accordance with ethical research standards for human subjects.

Our belief is that the publication of this work in Journal of Sports Science is part of the theme “Physical activity, Health and Exercise”, elucidating important issues of high relevance in the dissemination of information on immune modulation and the impact of lifestyle in individuals with distinct gender vaccinated against COVID-19.

The content presented and the submission of the manuscript to the Journal of Sports Science has been approved by all authors. The authors have not declared any conflicts of interest.

Your attention is appreciated, and we look forward to receiving your feedback.

Sincerely,

Ernesto Taketomi, MD, PhD

Laboratory of Allergy and Clinical Immunology

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3.1. Manuscrito

Adipokines and antibody response in individuals with levels of physical activity and sedentary behaviour following COVID-19 vaccination.

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Abstract: Sedentary behaviour in individuals may be associated with comorbidities and risk factors that contribute to immune system dysregulation, including obesity, type 2 diabetes, and cardiovascular diseases. Adipokines, cytokines released by adipocytes and immune cells within adipose tissue, play a pivotal role in modulating inflammatory responses. Elevated levels of pro-inflammatory cytokines are commonly observed in obese individuals and those with underlying comorbidities. This study aimed to investigate specific IgG levels following SARS-

CoV-2 vaccination and adipokine profiles in individuals with varying levels of physical activity and sedentary behavior, with focus on gender differences. Blood samples from 135 individuals selected based on strength tests and response to the International Physical Activity Questionnaire (IPAQ), were analysed. Levels of anti-S IgG, neutralizing antibodies, adiponectin, leptin, resistin, IL-10, and TNF- α were assessed. Individuals engaging in regular physical activity exhibited lower levels of leptin compared to their sedentary counterparts. Notably, women demonstrated higher levels of leptin and resistin compared to men, irrespective of physical activity level. However, adiponectin levels were significantly higher in women compared to men (5,099 pg/mL vs. 3,938 pg/mL, $p < 0.01$). Furthermore, women exhibited a greater production of IgG, with a lower index (0.52), compared to men with a higher index (0.76; $p < 0.0001$), suggesting potential gender-related differences in immune response. No significant differences were observed in other evaluated parameters. These findings underscore the significant impact of physical exercise and gender on COVID-19 vaccine-induced immunity, highlighting the importance of physical personalized vaccination strategies and targeted public health activity as an adjunct to vaccine efficacy. Understanding these mechanisms could be crucial for developing interventions tailored to diverse population groups based on behaviour.

Keywords: COVID-19, vaccine, physical exercise, adipokines, IgG.

1. Introduction

Sedentary behavior represents a significant risk factor for the onset and progression of numerous chronic diseases, including obesity, type 2 diabetes, and cardiovascular diseases (Arocha Rodulfo, 2019). Recent research has highlighted the multifaceted role of adipose tissue, traditionally regarded as an energy storage depot, in orchestrating systemic physiological processes through the secretion of bioactive molecules, known as adipokines (Gomez-Huelgas et al., 2019).

Adipokines, cytokines released by adipocytes and infiltrating immune cells within adipose tissue, exert pivotal roles in regulating energy balance and metabolism throughout the body. The diverse array of adipokines released from adipose tissue exerts both local and systemic effects via circulation (Pham, Nguyen, & Park, 2023; X. Wang, Zhang, & Li, 2023).

Adipocytes dynamically modulate cytokine secretion, which can either promote or attenuate inflammation depending on the local immune milieu and signaling cues. In a healthy state, T lymphocytes, particularly Th2, contribute to glucose homeostasis and enhance adipocytes insulin sensitivity, thereby promoting the activation of metabolically active brown adipose tissue. Conversely, in conditions of pathological inflammation, white adipose tissue predominates, initiating pro-inflammatory cascades and suppressing anti-inflammatory cytokine release (Clemente-Suárez et al., 2023; Recinella et al., 2020).

Leptin and resistin are prominent adipokines, known for their pro-inflammatory properties, by their ability to stimulate the production of TNF- α and IL-6 by monocytes (Ouchi et al., 2011). In contrast, adiponectin plays a crucial regulatory role in lipid metabolism and energy homeostasis, exerting anti-inflammatory effects. In addition, adiponectin exhibits protective effects on various cell types, enhances insulin sensitivity, and modulates metabolic processes. Reduced levels of adiponectin have been observed in individuals with several clinical conditions (Nguyen, 2020).

In obese individuals, adipokines released from adipose tissue play a pivotal role in the pathogenesis of metabolic disorders, contributing to the development of associated complications. Regular exercise has been demonstrated to mitigate the incidence of metabolic complications in this population (Ozcan et al., 2015; Zorena et al., 2020). Studies have revealed that obese women often exhibit leptin resistance and reduced serum adiponectin levels, which correlate with increased body mass index and adiposity (Lecke, Morsch, & Spritzer, 2011). However, interventions involving regular aerobic exercises have been shown to decrease leptin levels in obese women (Polak et al., 2006).

In this scenario, physically inactive individuals may show comorbidities and risk factors that induce immune system dysfunctions (Amin et al., 2021). These groups, during the COVID-19 pandemic, were taken with concern globally since they are prone to complications and increased severity of the disease with evolution to mortality and which immune responses to vaccinations have been ineffective (Damiot et al., 2020).

Throughout the pandemic, numerous countries have made significant strides in vaccine development against SARS-CoV-2, utilizing cutting-edge technologies such as mRNA (e.g., BNT162) and adenovirus vector (e.g., ChAdOx1) platforms (Eterafi et al., 2024). In Brazil,

both of these vaccine platforms were employed for mass vaccination campaigns, alongside the domestically manufactured inactivated viral vaccine CoronaVac (Sinovac), all of which received approval from government agencies and were administered to the public in 2021 (Firouzabadi et al., 2023). The widespread deployment of these vaccines aimed to enhance the safety and efficacy across diverse demographic groups, including individuals of all ages and those with underlying comorbidities, representing a critical strategy to mitigate disease incidence and reduce mortality risks (Chapman et al., 2022).

The immune response elicited by vaccines involves a cumulative effect of both cellular and humoral immunity, characterized by the activation of memory B and T lymphocytes orchestrated by a variety of cytokines and chemokines. This process leads to the production of specific antibodies targeting viral proteins, including IgG directed to the RBD region of the spike (S) protein. Additionally, the generation of blocking or neutralizing antibodies (NAbs) occurs, which possess the capacity to hinder viral cell infection by interfering with entry, fusion or viral release processes (Isho et al., 2020; Iwasaki and Watarai, 2020). The cellular immune response involves the activation of T CD4⁺ and T CD8⁺ cells, which release type 1 cytokines, such as IFN- γ and TNF- α , thereby promoting long-term immune responses and providing protection to vaccinated individuals against recurrent infections by the same pathogen (Ewer et al., 2021; Gálvez et al., 2022; M. Li et al., 2022). However, studies have indicated that following COVID-19 immunization, obese individuals exhibit lower antibody titers compared to the general population (Herzberg et al., 2022; Yamamoto et al., 2022). Furthermore, research has demonstrated that the levels of neutralizing antibodies against the virus significantly decrease after the third dose in individuals with severe obesity (Van Der Klaauw et al., 2023).

The modulation of immune responses can be observed in individuals engaging in physical exercises, resulting in a more effective response to vaccination. Clinical studies have indicated an association between the increased efficacy of influenza vaccine in individuals who regularly engage in chronic aerobic exercise compared to those who only engage in acute exercise (Bortolini et al., 2022). Additionally, research has shown that inactive individuals infected with SARS-CoV-2 are more susceptible to hospitalization and death compared to physically active individuals (Sallis et al., 2021). The immune mechanisms underlying how physical exercise can enhance the effectiveness of the immune response include the increase in T cells producing

anti-inflammatory cytokines and the reduction of pro-inflammatory cytokines and chemokines (Bortolini, et al., 2022). Furthermore, sedentary individuals who underwent interventions involving physical exercises exhibited higher titers of specific IgM and IgG antibodies against the influenza virus, leading to improved efficacy of the influenza vaccine in physical active individuals (Bachi et al., 2013; Campbell and Turner, 2018).

The reduction in the frequency of physical exercise globally, prompted by the COVID-19 pandemic, has had a significant impact on the quality of life. Social distancing measures and lockdowns have restricted access to gyms, parks, and other sports facilities, resulting in discontinuation of exercise routines. This has contributed to immune dysregulation, consequently increasing the risk of developing chronic diseases such as obesity, type 2 diabetes, cardiovascular diseases and osteoporosis (Bortolini, et al., 2022).

The distinct physiological conditions between men and women in relation to physical exercises have been shown to account for many findings in the general population, particularly in non-athletes. It is noteworthy that inactive women are more prone to cardiovascular diseases compared to men, regardless of age or social status (Amagasa et al., 2022). Moreover, studies have observed that sedentary behavior in women impairs cardiac modulation in response to physiological stress, compromising metabolic clinical parameters and increasing the risk of disease (Pines, 2015; Zaffalon Júnior et al., 2018). Several studies have focused on women's health, employing exercise interventions to assess adipokines in the context of metabolic disorders such as obesity, polycystic ovary syndrome, among others (Gomez-Huelgas, et al., 2019; Ozcan, et al., 2015; Souza et al., 2022). However, the role of COVID-19 vaccines in this regard has yet to be investigated. This study aims to assess the impact of adipokines on individuals of different genders who have been vaccinated against COVID-19 and engage in physical activity, compared to those who lead a sedentary lifestyle. This could provide clear evidence of whether physical activity can be considered a supportive factor in the production of neutralizing antibodies and IgG specific to the SARS-CoV-2 spike (S) protein. Such findings may enhance the potency of the immune response following vaccination and offer a protective effect. Assessing these attributes is essential for devising better vaccination strategies that prioritize specific groups and emphasize the significance of regular physical activity in enhancing immune responses for the prevention of chronic or infectious diseases.

2. Material and Methods

2.1. Study Design

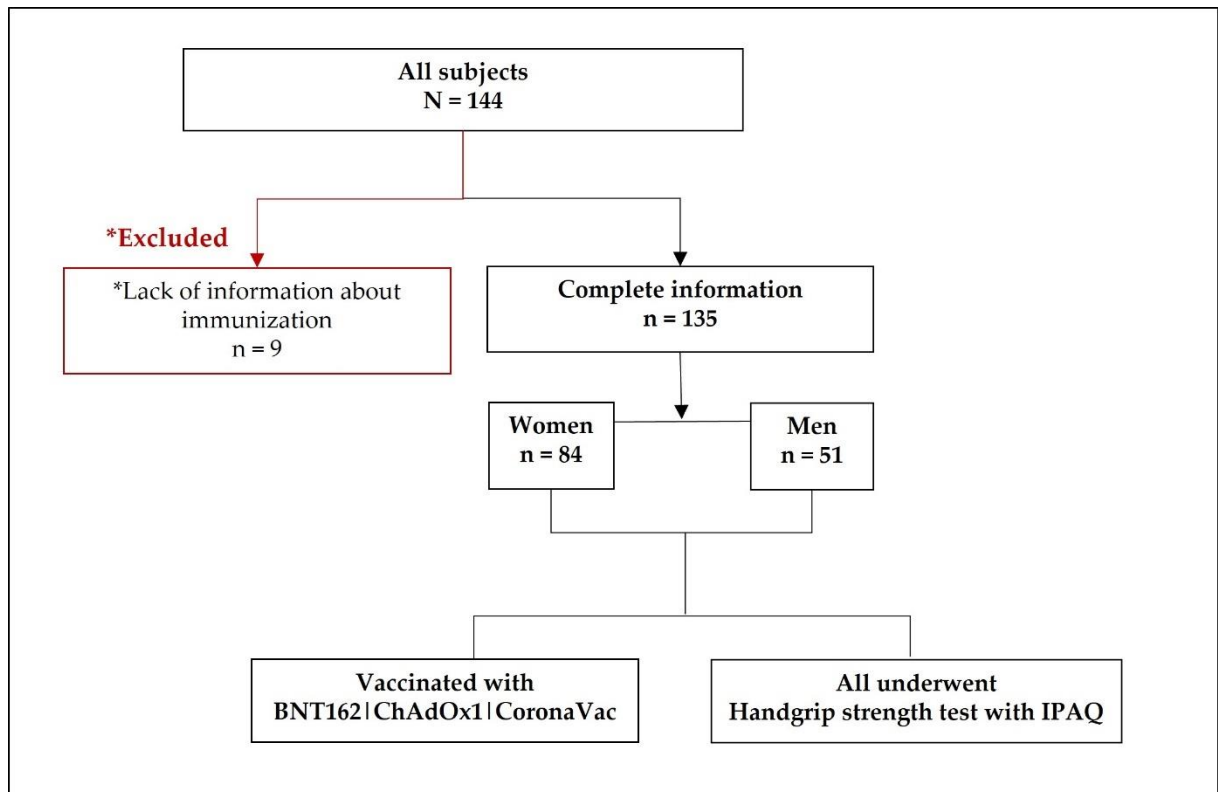


Figure 1. Flow-chart depicting the study design process, including participant selection and intervention procedures.

The study was conducted at the Clinics Hospital of the Federal University of Uberlândia, located in the southeastern region of Brazil, involving 135 volunteers aged 18 to 50 years who received the BNT162, ChAdOx1, or CoronaVac vaccines between July 2022 and September 2023. This vaccination protocol was based on the Brazilian Vaccination Program for COVID-19 in adults, which began in January 2021. The vaccine schedule consisted of two homologous doses (shot 1 and shot 2) administered at 8-week intervals for the monovalent BNT162 and ChAdOx1 vaccines, and at 28-day intervals for the CoronaVac vaccine. Additionally, a heterologous booster dose (shot 3) was included 16 weeks after shot 2. The research was

approved by the local ethics committee (Protocol CAAE-50001421.7.0000.5152 CEP/UFU), and informed consent was obtained from all participants prior to their inclusion in the study. Demographic data, including age and sex, along with vaccine-related information, such as the dates of the shots and the type of vaccine administered, were collected as part of the study protocol. Anthropometric measures were obtained, including body mass, height and body mass index (BMI).

Level of physical activity was determined by International Physical Activity Questionnaire (IPAQ) - Complete Form, in association with back-leg strength test. Individuals were divided into active/inactive groups based on the amount of time spent engaging in various activities, including work-related tasks, household chores, pet care, type of transportation for commuting, engagement in leisure physical activities, and sitting time.

2.2. Physical activity levels, anthropometric measures and strength test

Weight and height values were measured to determine the body mass index (BMI) using the formula Kg/m^2 , classified as follows: normal (18.5–25); overweight (25–30); obesity class I (30–35); obese class II (35–40); and obese class III (>40). The International Physical Activity Questionnaire (IPAQ) was also used to determine physical activity levels, as follows: low to sedentary behavior (SB) and moderate and high to practice physical activity (PA). The handgrip test (Saehan SH5001 Hand Dynamometer) was used to evaluate the strength of upper members. An adjustment of the equipment's phalanges was made, with settings of 1-2 for women and 3-4 for men, to ensure the correct force applied for each gender. Before, the participants were initially queried about presence of injuries or physical disabilities, subsequently, professionals demonstrated the correct position for equipment use and provided relevant information about repetitions and rest intervals. The test was conducted with individual seated in a chair with feet aligned on the floor, after hold the equipment with hands and right arm close to the trunk, the maximum force is recorded in kg/F upon squeezing the equipment, and the same procedure is repeated for the left arm. All individuals were tested three times with a rest interval of 1 minute between repetitions. During changing between equipment, the rest time was prolonged to 3 minutes. Throughout the test performance, the participant was encouraged to use their greatest force.

To assess body muscle strength, we calculated an index called FBMI, which is the ratio of the strength of the dominant arm to body mass. The formula for FBMI is given by: $FBMI = \text{force} / \text{BMI}$ whereas force was determined by the strength test, in kg/f, and BMI was determined by body mass and height (in kg/m²). This metric offers a more comprehensive and accurate evaluation of overall strength by accounting for variations in body type that could bias the study. Notably, higher FBMI values are associated with greater force levels.

2.3. Quantification of S protein-specific IgG

The evaluation of the humoral immune response for SARS-CoV-2 was determined by ELISA for detection of specific IgG antibodies to S protein in serum samples. The plates were sensitized with 0.2 µg/well of S protein (gently provided by Biomanguinhos, Fiocruz, Brazil). in 50 µL/well of phosphate-buffered saline solution (PBS), pH 7, 16h at 4°C. Then the plates were washed 5 times with PBS and blocked with 2% of skimmed milk per 1.3h at room temperature. The plates were washed again, and the serum samples of the individuals diluted at 1:40 in 1% block buffer (PBS + skim milk), were added and incubated for 2h in TA. The plates were washed again, and the secondary antibody conjugated with human anti-IgG HRP (ThermoFisher Scientific, Rockford, USA). was diluted with PBS and then added (1:60,000). The reaction was revealed by 3,3',5,5'-tetramethylbenzidine (TMB) (Sigma-Aldrich) for 10min and interrupted with the addition of 1N H₂SO₄. The optical density (OD) was determined in Multiskan FC spectrophotometer (ThermoFisher) and at 450nm wavelength.

2.4. Neutralizing antibodies (NAbs) against SARS-CoV-2

Following the manufacturer's instructions, the fluorescence-based LFIA (ECO Diagnóstica, Nova Lima, Brazil) was used to identify NAbs against the beta (B.1.351) and gamma (P.1) strains of SARS-CoV-2 in all three groups: vaccinated (V), unvaccinated/convalescent (UC), and unvaccinated/naïve (UN). A microtube was filled with 100 µL of serum samples, 200 µL of extraction buffer, and lyophilized beads containing ACE-2/biotin and RBD/europium recombinant proteins. The microtube was then incubated at 37°C for 20 minutes. The test cassette was then filled with 100 µL of each mixture. The mixture was then allowed to incubate for a further 15 minutes at room temperature, after which the findings

were shown. Using the supplied reader (F200 Fluorimeter, ECO Diagnóstica), the fluorescence intensity was measured. An inhibition index more than 20% suggested the existence of NAbs.

2.5. Quantification of adipokines and cytokines by ELISA

Adipokines (adiponectin, leptin, and resistin) were measured according to the manufacturer's procedure using ELISA kits (R&D Systems, San Diego, USA). In summary, 100µl of capture-specific monoclonal antibodies were applied to high protein affinity ELISA plates for the intended targets, and the plates were then incubated at 4 for 12–16hs. Following this procedure, the plates were locked for four hours at room temperature using 200µl of BSA PBS 1% and cleaned three times using PBS/Tween 0,05%. Serum samples (adiponectin: 1/2000, leptin: 1/50, and resistin: 1/25) were diluted and added (100 µL) for an 18-hour incubation period at 4°C. The biotinylated detection secondary antibody was added and incubated for an additional three hours at room temperature following another washing. After another wash, the plates were incubated for 60min at 37°C with a streptavidin conjugated to peroxidase (1.25 ng/mL). Tetramethylbenzidine (TMB) was added for reaction development following washing cycles, and after 10min, 2% H₂SO₄ was added. The absorbance was then measured using an Enspire Multimode Plate Reader (ELISA) at a wavelength of 450nm. By comparing the samples to a standard curve created using the corresponding recombinant proteins, each of which was used in a different serial dilution, the concentration of the samples was determined.

Levels of pro-inflammatory and anti-inflammatory cytokines (IL-10 and TNF-α) were determined using BD-specific kits (BD Biosciences), following the manufacturer's protocol. In summary, high-affinity plates were coated with specific monoclonal capture antibodies for the targets of interest and incubated for 12-16h at 4°C. After washing the plates with PBS/Tween 0.05%, they were blocked with PBS BSA 1% at room temperature for 4 hours. The samples or standard curve of the targets were then added in duplicate and incubated for 18h at 4°C. After washing, was added biotinylated secondary antibody and incubated for 3hs at room temperature, followed by the addition of conjugated peroxidase to streptavidin and incubation for 20min at 37°C. The TMB reagent was added to color development, which was stopped with 2% H₂SO₄. The absorbance was measured at 450nm in an Multiskan FC Microplate

Photometer. The concentration of the samples was estimated by comparison with a standard curve.

2.6. Statistical analysis

All data were assessed with GraphPad Prism software version 9.4.0 (GraphPad, San Diego, USA). Data were analyzed considering the number of variables (Student's t-test for two variables or One-way ANOVA for more than two variables) according to the distribution pattern to Kolmogorov-Smirnov normality test.

To analyze the relationship between variables, specific methods were used according to the distribution of data. Pearson correlation was used for data that follow a normal distribution, while Spearman correlation was used for data that do not follow this distribution. To compare two different groups, the Mann-Whitney test was performed. For the evaluation of significant results, the value of $p < 0.05$ was considered.

3. Results

3.1. Demographic data of the participants

The study initially counted on the enrollment of 140 individuals according to the defined inclusion criteria. However, during the data collection procedure, due to loss of information, the sample decreased to 135 individuals. The information on demographic, anthropometric and mean strength data are described in the Table 1.

Table 1. Demographic and physical characteristics of the individuals.

Characteristic	Men (n = 51)	Women (n =84)	p
Individuals (%)	38%	62%	0.0381*
Age (years, mean ¹)	26.5±7.9	26.4±7.2	0.8729
Body mass index (BMI, mean ¹) kg/m ²	23.9±4.7	23.6±4.7	0.9414
FBMI (mean ¹)	3.9±1.2	2.0±0.6	0.0001*
Physical activity (PA)	27 (52,9%)	35 (41,7%)	0.2173
Sedentary behavior (SB)	24 (47%)	49 (58,3%)	
Handgrip dominant arm (mean ¹ , kg/F)	41.6±8.8	26.8±6.0	0.0001*
Handgrip non-dominant arm (mean ¹ , kg/F)	39.2±9.4	24.7±5.7	0.0001*

¹ Mean and standard deviation; * $p < 0.05$ considered significant

The study participants were predominantly female, representing 62% (n = 84), while males made up 38% (n = 51) of the total. The homogeneity analysis was performed using the Student's t-test. The mean age of men was 26.5 years and women 26.4 years. In addition, the average BMI to women was 24.4 kg/m² and to men 24.3 kg/m². Regarding handgrip strength, the values showed variations according to the sex of the individuals, the dominant arm of 41.6 kg/F for man and 26.8 kg/F for woman (p<0.0001), the non-dominant arm to man was 39.2 kg/F and for woman 24.7 kg/F, which is expected that women have less strength than men (Figure 2A). Within the group of women there was no significant difference in strength and FBMI between PA and SB (p=0.3771; p=0.3559) (Figure 2B), the same was observed in the group of men (p=0.4622; p=0.6017) (Figure 2C). The mean of the dominant arm and non-dominant arm was calculated and the result was used to compare the amount of force (kg/F) that each individual was able to achieve according to their classification by IPAQ (Figure 2).

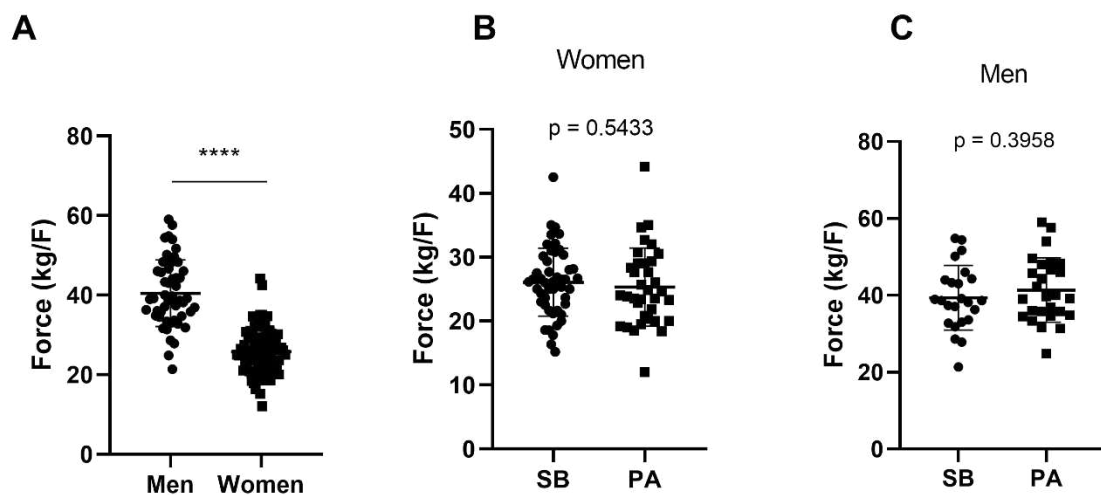
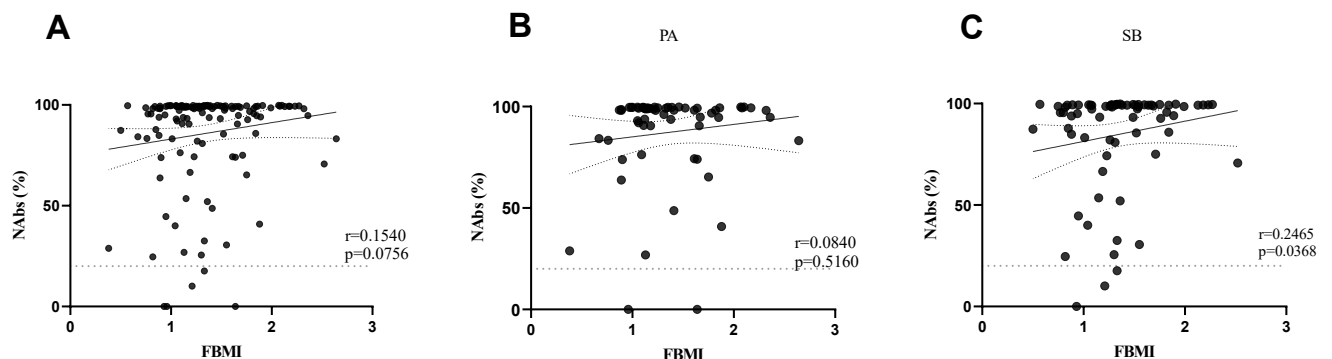


Figure 2. Strength patterns in men and women categorized by physical activity (PA) or sedentary behavior (SB), as determined by the International Physical Activity Questionnaire (IPAQ). hand grip dynamometer test. **(A)** Force intensity comparison between men and women. **(B)** Force intensity comparison among women. **(C)** Force intensity comparison among men. Force (Kg/F) represents the mean values of handgrip strength, measured in both right and left arms. Unpaired t- test used and significance indicated by ***p <0.0001.

3.2. Correlation of levels of anti-S IgG and NAbs in the group of PA and SB individuals regardless of gender.

The correlation between neutralizing antibodies was evaluated in relation to the FBMI index and anti S IgG with FBMI, to assess whether the overall strength of the individual actively influences the production of antibodies (Figure 3). There were no significant correlations between the variables NAbs and FBMI ($r=0.1540$; $p=0.0756$) and anti S IgG and FBMI ($r=0.1478$; $p=0.0871$) in both groups (Figure 3A and 3D). In addition, stratifying the population between PA and SB by IPAQ, the same correlation was performed (Figure 3). There was no correlation in the PA group among NAbs and FBMI ($r = 0.0845$; $p = 0.5160$) (Figure 3B) and also anti S IgG and FBMI ($r=0.2150$; $p=0.0933$) (Figure 3E). However, in SB group, it was possible to observe a weak positive correlation ($r=0.2465$; $p=0.0368$) between NAbs and FBMI (Figure 3C) but not in the levels anti S IgG and FBMI ($r=0.0880$; $p=0.4588$) (Figure 3F).



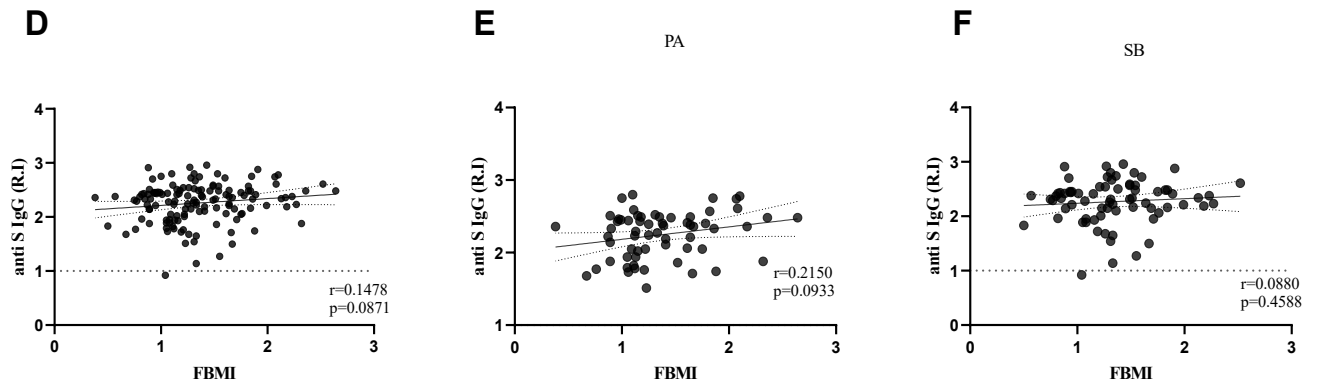


Figure 3. Correlation between Fat Body Mass Index (FBMI) and Neutralizing Antibodies (Nabs), as well as between FBMI and anti-S (Spike) IgG levels, assessed in the overall study population. Subgroup analyses were conducted for the Physical Activity (PA) and Sedentary Behavior (SB) groups. (A) General NAbs correlation (B) NAbs correlation in the PA group (C) Nabs correlation in the SB group (D) General anti-S IgG correlation (E) Anti-S IgG correlation in the PA group. (F) Anti-S IgG correlation in the SB group. The horizontal dashed line indicates the threshold of positivity (Nabs < 20 and IgG < 1.2). Correlations were assessed using Spearman's test and significant values of $p < 0.05$ were determined.

Regarding the levels of anti-S IgG antibodies, a comparison was performed between the means of the ratio between FBMI index on IgG in woman and man, to evaluate the influence of global force on the production of antibodies specific to the virus S protein (Figure 4). A significant difference ($p < 0.0001$) was observed between both sexes, where high FBMI/IgG ratio index represent lower IgG production in response to vaccination. In this sense, women represented a greater trend in the production of vaccine antibodies.

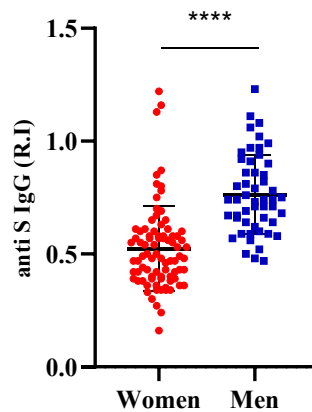


Figure 4. Anti-S IgG serum levels in men and women. Ratio between FBMI index on IgG in woman and man, the lower the FBMI/IgG ratio, the higher the production of anti S IgG. *** $p < 0.0001$. Unpaired t test used with significance $p < 0.05$.

3.3. Quantification of cytokines and adipokines in the different stratified groups.

For the evaluation of adipokine levels between men and women, we observed significant differences in leptin in the general population between men and women ($p < 0.0001$) (Figure 5A), in the PA group (Figure 5B) and in the SB group ($p < 0.0001$) (Figure 5C). Regarding resistin, women presented the same pattern, with a significant increase in this adipokine compared to men ($p < 0.01$) (Figure 5D), there were no significant differences in the PA and SB group ($p = 0.0991$; $p = 0.0838$), although 3 men individuals produce more resistin (Figure 5E and 5F). Although there is a tendency of women in general both active and sedentary present the same behavior in the production of resistin. However, although women have high levels of pro-inflammatory adipokines, adiponectin levels were increased in women compared men the general population ($p < 0.0001$) (Figure 5G). Although not significant in the sedentary behavior group ($p = 0.0541$) (Figure 5I), suggesting a pattern of regulation of the organism itself to compensate for the inflammatory process.

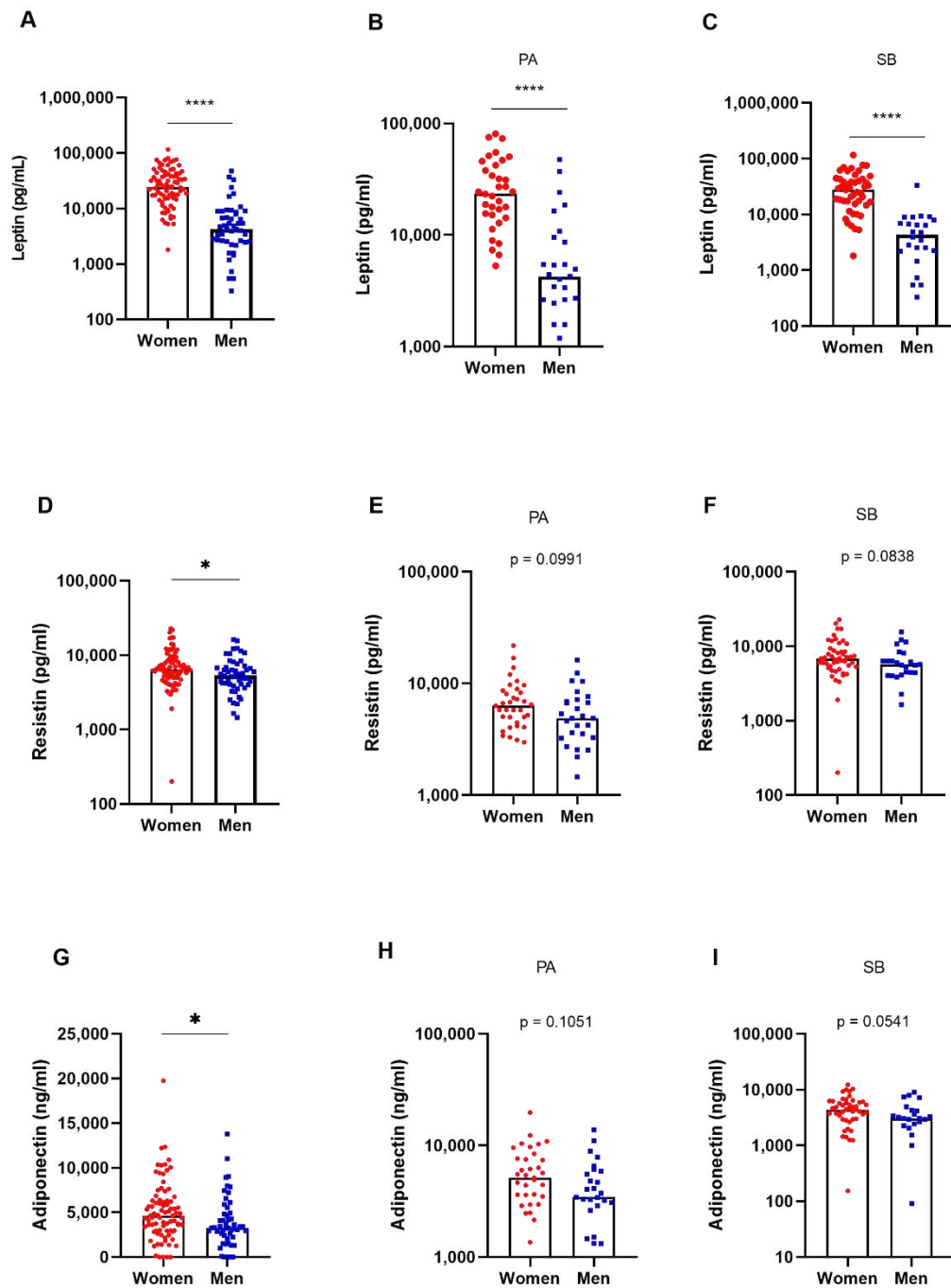


Figure 5. Comparison of adipokines serum levels between men and women in the general population, physical activity (PA) group, and sedentary behavior (SB); leptin (A) (B) (C); resistin (D)(E)(F); adiponectin (G) (H) (I) * $p < 0.01$ **** $p < 0.0001$. Mann-Whitney test considered significant $p < 0.05$, the data are represent in median.

To assess the impact of adipokine production in both genders and whether it influences one another, a comparison of the means of the ratios between leptin, resistin, and adiponectin in men and women was made with regard to adipokine levels (Figure 6). A significance difference ($p < 0.0001$) was observed between both sexes to each adipokines, where high leptin/resistin ratio represent lower resistin production in women in comparison men (Figure 6A), also observed the same tendency to leptin/adiponectin ratio with lower adiponectin in women (Figure 6B). However, how expected low resistin/leptin ratio (Figure 6C) and adiponectin/leptin ratio (Figure 6D) represent in both results higher leptin production in women compared men.

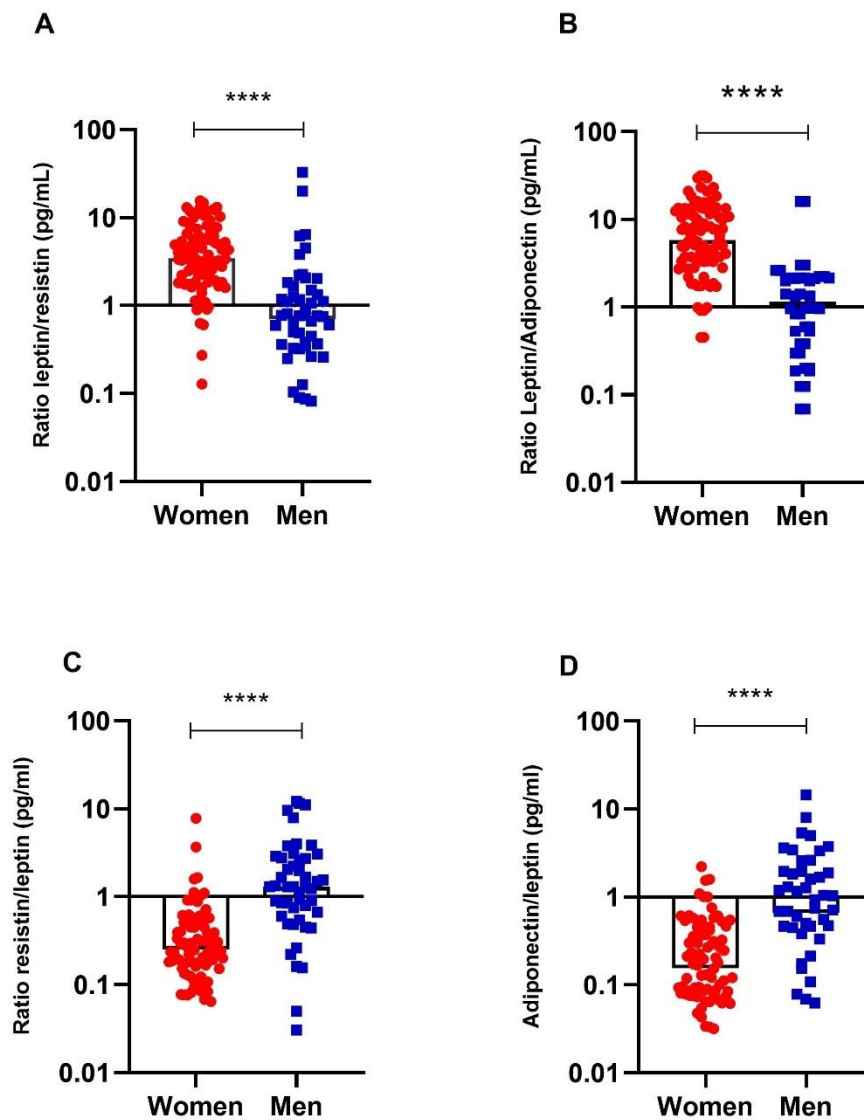


Figure 6. Comparison of adipokines serum levels between men and women in the general population. Ratio between leptin and resistin (A) leptin and adiponectin (B) resistin and leptin (C) and adiponectin and leptin (D). **** $p < 0.0001$. Mann-Whitnet test considered $p < 0.05$ significantly.

In this regard, we assessed whether sedentary behavior and physical exercise affected the levels of all adipokines, or whether women's production was higher than that of men's (Figure 7). Because the ratio of leptin/resistin was lower in contrast to women, the ratio among

adipokines was realized and differences in resistin levels were identified in both the sedentary and active males groups (Figure 7A). Men produced more adiponectin than women did in the PA and SB group, as indicated by the considerably lower ratio of leptin/adiponectin (Figure 7B). Men produced more adiponectin than women did in the PA and SB group, as indicated by the considerably lower ratio of leptin/adiponectin (Figure 7B).

Confirming previous findings, the ratio of resistin/leptin (Figure 7C) and the ratio of adiponectin/leptin (Figure 7D) were higher in the women group with physical activity and sedentary behavior. Men, on the other hand, had lower levels of leptin compared to women, regardless of their physical activity or sedentary behavior. However, it was observed that the ratio of adiponectin/leptin varied in the five men group, indicating differences in leptin production. These variations were not observed in the women group, suggesting that leptin production is influenced by gender.

(A) Leptin/Resistin



(B) Leptin/Adiponectin



(C) Resistin/Leptin



(D) Adiponectin/Leptin



Figure 7. Comparison of adipokines serum levels between men and women in the general population. Ratio between leptin and resistin (A) leptin and adiponectin (B) resistin and leptin (C) and adiponectin and leptin (D). *** $p < 0.0001$. Mann-Whitney test considered significant $p < 0.05$, the data are represent in median.

Adipokine levels and FBMI index were correlated. When analyzing the relationship between leptin and FBMI, a negative correlation was observed, suggesting that the higher the FBMI index, the lower the leptin levels ($r = -0.4167$; $p < 0.0001$) (Figure 8A). Nevertheless, there was no correlation between resistin ($r = -0.0872$; $p = 0.3142$) and adiponectin ($r = -0.1537$; $p = 0.0752$) compared to FBMI levels. When the sample was stratified into groups PA and SB the leptin levels, the results revealed a negative and statistically significant correlation between in physical active participants ($r = -0.4778$; $p < 0.0001$) (Figure 8B) sedentary behavior participants ($r = -0.3744$; $p = 0.0011$) (Figure 8C). These findings suggest that the more active the individual, the lower their serum leptin levels

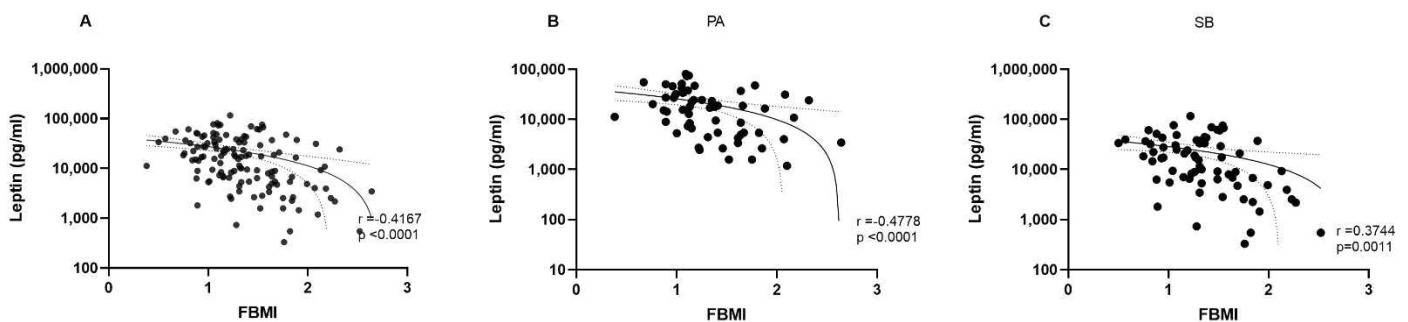


Figure 8. Correlation between the fat-to-body mass index (FBMI) and (A) Leptin serum levels in the general population; (B) leptin serum levels in the physical activity (PA) group; (C) leptin serum levels in the sedentary behavior (SB) group. Correlation was determined using Spearman's test, with significant values of $p < 0.05$.

Furthermore, the objective was to evaluate the production of proinflammatory cytokine of the participants in relation to the FBMI index. For this, the ratio between the levels of the FBMI index and $\text{TNF-}\alpha$ ($\text{FBMI}/\text{TNF-}\alpha$) was calculated and correlated with the ratio between the FIMC index and IL-10 levels ($\text{FBMI}/\text{IL-10}$). The study population was divided into groups of active and sedentary participants, where no correlations were found between inflammation levels and the FBMI index in active individuals (Figure 9). However, in sedentary individuals,

a moderate positive correlation was observed ($r=0.3023$; $p=0.0093$), although some individuals are scattered.

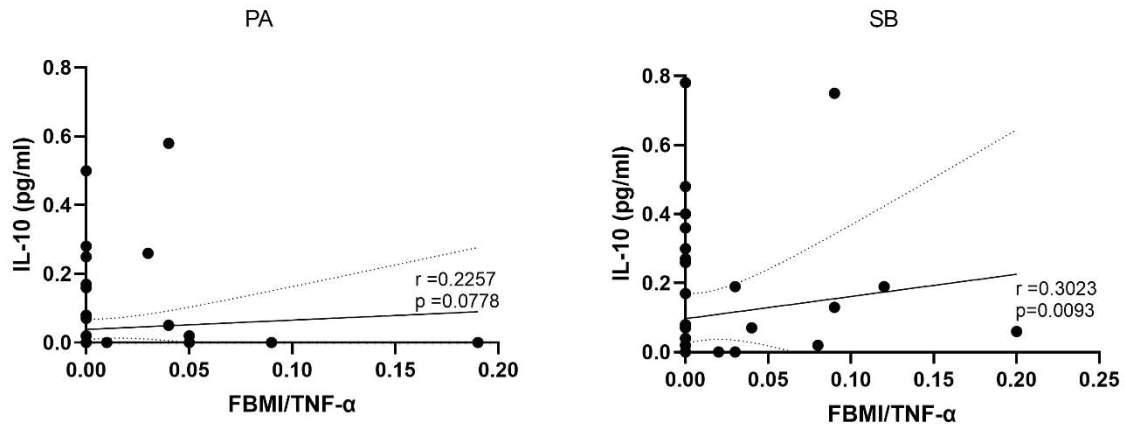


Figure 9. Correlation between the fat-to-body mass index (FBMI) and (A) Ratio FBMI/TNF- α and IL-10 serum levels in the physical activity (PA) (B) Ratio FBMI/TNF- α and IL-10 serum levels in the sedentary behavior (SB). Correlation was determined using Spearman' s test, with significant values of $p < 0.05$.

To evaluate the correlation between strength, determined by the FBMI index, and levels of antibodies and cytokines, the Spearman correlation test was conducted, and the results were presented by means of a correlation matrix (Figure 10).

The results indicated a negative correlation between leptin levels and FBMI ($r=-0.417$; $p<0.0001$), as well as between resistin levels and IgG anti S ($r= -0.200$; $p= 0.02$). In addition, a weakly positive correlation was observed between TNF- α and FIMC ($r= 0.178$; $p= 0.039$), and between leptin and resistin ($r= 0.168$; $p= 0.051$).

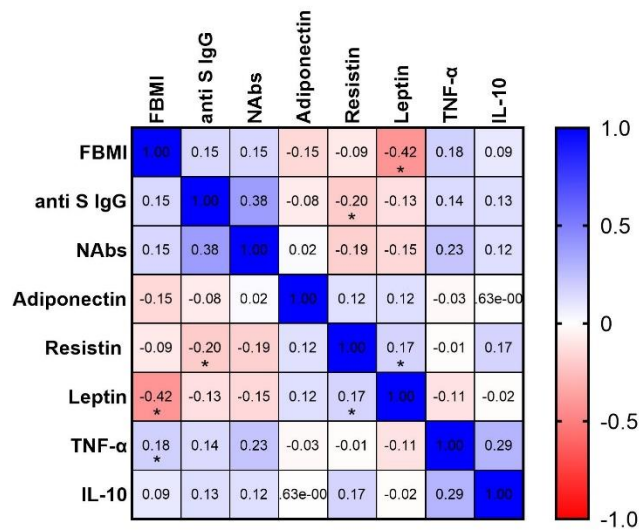


Figure 10. Correlation analysis among all study variables in the general population.

4. Discussion

This study aimed to investigate the interplay between physical activity patterns and adipokine production, with a focus on their potential impact on immune response modulation following COVID-19 vaccination among both genders. Participants received vaccinations in accordance with the official Brazilian immunization schedule outlined by the National Immunization Program of the Ministry of Health, which included three vaccine doses, including a booster dose. However, due to the study's cross-sectional design, the varying time intervals between vaccine administration and blood sample collection during participant recruitment represent a notable limitation. Nonetheless, the presence of neutralizing antibodies in the majority of individuals underscores significant protective efficacy, largely attributed to vaccination, as all participants underwent vaccination procedures. Studies have demonstrated that levels of neutralizing antibodies remain elevated, providing significant protection for up to six months post-infection. Conversely, at the three-month mark post-vaccination, these findings remain consistent, confirming the vaccine's protective efficacy, thereby corroborating the observations made in this study (J. Wang et al., 2023).

In terms of the handgrip test, a notable disparity in force was observed between the dominant and non-dominant arms, with the dominant arm exhibiting approximately 10%

greater force compared to the non-dominant arm. This discrepancy suggests that men individuals generally possess greater manual strength in their dominant arm compared to women. These results align with prior research findings, thus reaffirming the existing gender-related differences (Amaral et al., 2019; Andrade Fernandes et al., 2014).

The International Physical Activity Questionnaire (IPAQ) was utilized to classify participants into physical activity and sedentary behavior categories. While it serves as a valuable tool, evidence indicates a potential bias in its validity, primarily stemming from the questionnaire's tendency to underestimate sedentary behavior (Oliveira et al., 2023). Furthermore, the IPAQ has been observed to overestimate reported physical activity levels compared to actual activity levels, as documented in previous studies (Lee et al., 2011; Ryan et al., 2018). In this study, the IPAQ proved to be insufficiently sensitive in distinguishing between sedentary behavior and active individuals. Instead, the dynamometer strength test was employed in tandem with the body mass index (BMI) to evaluate performance and categorize participants. This association gave rise to the development of the FBMI index, the basis of which may be found in prior studies. For instance, the maximum repetition test (1 RM) often serves as a metric for assessing muscle strength, enabling the estimation of a pattern based on reactive strength, accounting for the body mass index and, thereby identifying the individual maximum strength level (Teixeira et al., 2019). Our study highlighted the utility of FBMI as a reliable indicator, calculated by dividing the weight reached in the handgrip test by the BMI, which accounts for the height and mass of the individual, mitigating potential variances observed in the biotypes of the study volunteers.

BMI serves as a cost-effective anthropometric tool for estimating overweight and obesity. Providing an indirect measure of body fat when compared, for instance, with bioelectric impedance (Nigro et al., 2023). However, in the absence of the later tool, FIMC proved to be a practical technique for minimizing observed discrepancies and facilitating the evaluation of overall strength in individual. Future research endeavors focusing on fat percentage assessment will be necessary to elucidate the impact of obesity and excess fat on the immunological response to COVID-19 vaccination.

Physical activity plays an important role in boosting nitric oxide (NO) levels through adenosine monophosphate (AMP) triggering the protein kinase signaling pathway (MAPK). This increase has been shown to result in a reduction in SARS-CoV-2 viral multiplication, suggesting an immunoprotective benefit during infection (Papadopoulos, Sutheesophon, & Aw, 2022).

Additionally, another study revealed an association between individuals who engage in chronic physical exercise and a higher level of antibody development in response to the influenza vaccine. This study also suggested a potential relationship between vaccine immune response and the age and sex of individuals (Dinas et al., 2022).

During the pandemic, a decline in the level of physical activity was observed in the general population, with sedentary behavior tripling compared to pre-pandemic levels. This shift towards sedentary behavior was particularly notable in the female population, as documented in previous research, which may indicate a significant impact on the immune response to vaccination (Mulasso et al., 2023). Interestingly, IgG levels did not exhibit a significant correlation with the FIMC index in our study, consistent with previous findings, suggesting that chronic exercise does not influence baseline levels of IgG (Drummond et al., 2022). However, other studies have indicated that physical exercise can improve the immune response to vaccines such as Pneumovax-23 in physically active individuals, acting as a coadjuvant in this process (Campbell and Turner, 2018). In this study, no significant correlation was found between NAbs levels and the FIMC index in the general population. However, upon specific analysis of sedentary individuals, both women and men, a significant correlation was observed, suggesting that the sensitivity of the test used may influence these results. Currently, the plate reduction neutralization test (PRNT) is considered the gold standard for evaluation neutralizing antibodies. Widely employed in research laboratories, it boasts high sensitivity in detecting these antibodies. However, it requires the use of biosecurity level laboratories compatible capable of culturing the virus and/or related particles (Vaidya, 2023; Valcourt et al., 2021). In this study, a point-of-care test (POCT) approach was used to quantify the levels of neutralizing antibodies, owing to restricted access and the limitations of the PRNT method. Additional research indicates that the correlation between NAbs and anti S IgG is utilized as a prognostic indicator for assessing the effectiveness of the immune response, without the need for complex NAbs testing (Hachmann et al., 2022).

Regarding the serum level of IgG specific to the protein S, a statistically significant difference was identified, with female subjects exhibiting higher titers of this antibody compared to males. These results findings align with previous studies, which also demonstrated a better ability of women to produce more antibodies in response to vaccination compared to men (Papaioannidou et al., 2023). This association can be partially attributed to hormonal factors, primarily in young women. The hormone estrogen plays a protective role against SARS-CoV-2 infection by

modulating inflammation within the signaling network of the individual's immune system (F. Li et al., 2022). Additionally, estrogen can increase the antiviral resistance of cells, reduce the production of pro-inflammatory cytokines, and promote the synthesis of antibodies by B cells, characteristics that corroborate the results of this study (Averyanova et al., 2022).

However, testosterone may act as a suppressor of the immune response to the COVID-19 vaccine, as men exhibit impaired IgG production. These results are in line with other studies that highlight the immunosuppressive role of this hormone in antibody production in vaccines against influenza, attributed to the upregulation of anti-inflammatory cytokines synthesis. In contrast, women tend to exhibit a higher production of proinflammatory cytokines, such as leptin and IL-6, for example, findings also observed in this study (Furman et al., 2014).

The increase in adipokines in women is due to the high amount of adipose tissue, although other investigations have shown that obese men have higher leptin production that can be influenced by lower testosterone (Pallio, 2023; Hoffman and Valencak, 2021).

In this regard, our investigation revealed a disparity in leptin levels between women, who produce a greater quantity of leptin compared to men, regardless of their level of physical activity. This phenomenon may be attributed to the inhibition of leptin expression by testosterone and its stimulation by ovarian sex steroids (Childs et al., 2021; La Cava, 2017). Furthermore, a clear association between leptin and the FIMC was observed in the sedentary group, which could be attributed to the higher proportion of sedentary women in this group. Previous studies have demonstrated an association between leptin and sedentary behavior and have also found a direct correlation between high leptin levels and the incidence of SARS-CoV-2 infections (Nigro, et al., 2023).

Regarding resistin, its inflammatory function has been observed in patients infected with the virus who exhibit more severe manifestations of the illness. This occurs due to the activation of this adipokine, which leads to the production of additional pro-inflammatory cytokines and adhesion molecules (Nigro, et al., 2023). Research indicates that during long-term physical activity, the concentration of resistin in the blood decreases (Jones et al., 2009). In this study, it was found that women had higher levels of resistin compared to men. This can be attributed to the fact that most women lead a sedentary lifestyle, which contributes to obesity and metabolic illnesses. These conditions further elevate the levels of resistin (Alissa, Alzughairi, &

Marzouki, 2019; Marcelino-Rodríguez et al., 2017). Previously, increased resistin levels were observed in women with polycystic ovarian syndrome, a variable that was not investigated in the study (Panidis et al., 2004). It is crucial to highlight that both adiponectin and resistin are directly linked to insulin sensitivity, which is influenced by diet. Adiponectin is associated with increased insulin sensitivity, whereas resistin is linked with a decrease in insulin sensitivity (Giandalia et al., 2021; Jones, et al., 2009).

Adiponectin, a cytokine whose expression is inversely proportional to BMI, exhibit anti-inflammatory characteristics. However, research has shown a duality in its actions, suggesting that this cytokine might contribute to inflammatory conditions, impacting the etiology of numerous disorders. Regarding COVID-19, a lower expression of this adipokine has been identified in patients with more severe manifestations of the condition (Nigro, et al., 2023). Additional studies indicate that moderate exercise paired with a regulated diet can alter adipokine levels, reducing leptin and raising adiponectin (Khalafi et al., 2023).

In addition to adipose tissue, other tissues such as muscles can produce cytokines, known as miocins, which play important roles in the regulation of inflammation. Due to this, the production of these cytokines by the muscle may have influenced the result found in this study (Ren et al., 2022).

In the analysis of the degree of inflammation of individuals, a strong association was identified between the cytokines IL-10 and TNF- α . Previous investigations indicated significant reductions in serum TNF- α levels following treatments, although there were no changes associated to regular physical exercise were observed (Shobeiri et al., 2022). Additionally, research has shown that IL-10 is a cytokine with high pleiotropic capacity, which can act as a pro-inflammatory molecule and induce the activation of the immune system, stimulating the production of other pro-inflammatory cytokines and the proliferation of T cells (Carlini et al., 2023; Najafi-Fard et al., 2022). These correlations between cytokines suggest that sedentary individuals may exhibit a higher pro-inflammatory response compared to active counterparts. This could be attributed to the fact that, despite the apparent balance between these cytokines, IL-10 may have an inflammatory role in this environment, a parameter that was not investigated in this work. The reason for the weak correlation between TNF- α and IL-10 in our results may

stem from some individuals lacking the ability to detect these cytokines due to their low serum levels.

5. Conclusions

This study suggests that physical exercise can positively impact the immunological response elicited by the COVID-19 vaccine. In addition, gender emerged as a key component in the evaluation of strength, cytokine levels, and antibody production, as hormonal variations may directly influence these factors. The findings based on the FIMC index revealed that active individuals had lower levels of leptin compared to sedentary counterparts. However, in terms of inflammation, the opposite trend was observed. These findings highlight the relevance of physical activity in modulating proinflammatory cytokines, which could significantly impact the effectiveness of the immune response to vaccination. Therefore, future studies incorporating behavioral, molecular, and immunological approaches will be essential to elucidate the mechanisms underlying this relationship. Moreover, the adoption of more sensitive methods for detecting markers, assessing the physical state of individuals, and addressing the heterogeneity of the sample population will be crucial for advancing our understanding in this area.

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Disclosure statement

No conflicts of interest have been declared by all the authors.

Data availability statement

The authors can provide access to the raw data that backs up the conclusions of this article upon request.

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4. Exercícios físicos na alergia respiratória

Manuscrito a ser submetido na revista Expert Review of Respiratory Medicine - Editora Taylor & Francis (Fator de Impacto: 3,9), com previsão da submissão em julho de 2024.

4.1. Carta de apresentação: *Expert Review of Respiratory Medicine*

Prof. Joseph Blondeau

Editor-in-chief

Expert Review of Respiratory Medicine, Taylor & Francis

Royal University Hospital Room 3736, Saskatoon SK, Canada

Dear Prof. Joseph Blondeau,

*I would like to submit for your consideration the manuscript entitled “**Physical activity, sedentary behavior, and adipokines production in atopic individuals with allergic rhinitis**” for consideration in form of Original Research, with authorship of Laura Alves Ribeiro Oliveira, Alessandro Sousa Correa, Leticia Cardoso Martins, Marielle Máximo Barbosa Chamberttan Souza Desidério, Wesley Guimarães Bovi, Carlo José Freire de Oliveira, Virmondes Rodrigues Júnior, Miguel Junior Sordi Bortolini, Rafael de Oliveira Resende, and Ernesto Akio Taketomi, for publication on *Expert Review of Respiratory Medicine*.*

This manuscript represents a study with atopic individuals with active and sedentary behavior, which were recruited based on their predisposition to produce specific IgE for respiratory aeroallergens, in addition to symptoms of allergic rhinitis. The results demonstrated that the atopic individuals produce less leptin levels compared to non-atopic individuals, independent of lifestyle. In atopic individuals with physical activity, there is a reduction in adiponectin, an anti-inflammatory cytokine in healthy people. In contrast, adiponectin modulated immune response in non-atopic individuals, based on rhinitis symptoms. The specific-HDM IgE and score of rhinitis are correlated with leptin levels and this relationship has not been described in the literature to date.

We declare that the article is original and has not been published in any other scientific journal. This study was conducted following ethical research standards in human subjects.

*We believe that the publication of this work in *Expert Review of Respiratory Medicine* may contribute to the dissemination of relevant information the impact the intervention of physical activity the field of respiratory allergies.*

All authors are aware of the work and agree with the content presented and submission of the manuscript to the Expert Review of Respiratory Medicine and declare total absence of conflict of interest.

We appreciate your attention and anticipate receiving your feedback.

Sincerely,

Ernesto Taketomi, MD, PhD

Laboratory of Allergy and Clinical Immunology

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4.2. Manuscrito

Physical activity, sedentary behavior, and adipokines production in atopic individuals with allergic rhinitis: exploring associations with symptom severity and IgE production

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Abstract: Patients with allergic rhinitis (AR) have symptoms such as sneezing, nasal congestion, and itching, triggered by aeroallergens, such as house dust mites (HDM), pet hair, grass pollens, among others. Sedentary behavior (SB) can contribute to obesity, potentially exacerbating allergy disorders, while physical activity (PA) may offer relief, mediated by adipokines. This study aimed to assess adipokines levels and physical activity in atopic patients (AT) concerning the severity of AR symptoms, compared to a non-atopic (NAT) control group. A total of 303 individuals were recruited, comprising 162 AT and 141 NAT, all underwent skin prick test (SPT) and/or HDM-serum specific IgE. Within AT group, 81 in PA and 81 in SB; while in the NAT group, 66 in PA and 75 in SB, based on strength tests and the International Physical Activity Questionnaire (IPAQ). Adipokines levels, including leptin, resistin, and

adiponectin were assessed. The AT group showed a significant higher index of HDM-specific IgE (1.7) than NAT group (0.7) ($p < 0.0001$). No significant differences were found between the PA and SB subgroups within each group ($p = 0.6722$; $p = 0.6838$). Although low levels of leptin were observed in AT group (16,474 pg/mL) compared NAT group (21,178 pg/mL) ($p < 0.001$), no significant differences were found in resistin and adiponectin levels between the two groups. The AT/PA subgroup exhibited a smaller Rhinitis Control Assessment Test (RCAT) score (15) compared to the AT/SB subgroup (18), suggesting that PA was associated with fewer symptoms compared to SB ($p < 0.05$). The AT/PA subgroup showed high levels of adiponectin (4,936 ng/mL) compared AT/SB subgroup (3,688 ng/mL) ($p < 0.05$). However, the AT/SB subgroup showed higher levels of adiponectin in individuals with severe (4,076 ng/mL) than mild symptoms (2,856 ng/mL) compared to AT/PA subgroup ($p < 0.05$). No significant differences were observed between in other adipokine levels between the two subgroups with respect to symptom severity. The BMI was evaluated alongside adipokine levels, revealing that obese AT individuals had higher levels of leptin (26,042 pg/mL) compared to non-obese AT (10,276 pg/mL) ($p < 0.05$). Positive correlations were found among HDM-specific IgE, RCAT score ($r = 0.48$; $p < 0.0001$), serum leptin, and BMI ($r = 0.22$; $p = 0.007$), as well as with PA and adiponectin with resistin ($r = 0.33$, $p = 0.03$). In the SB subgroup, positive correlations were observed between leptin and BMI ($r = 0.26$, $p = 0.02$). Additionally, a weak inverse correlation was seen between adiponectin and RCAT score ($r = -0.18$, $p = 0.02$), as well as between leptin levels and FBMI ($r = -0.32$, $p < 0.0001$). Among PA individuals, a negative correlation was observed between leptin levels and symptom severity score (SSS; $r = -0.26$, $p = 0.02$) while among SB subgroup, a negative correlation was observed between adiponectin and SSS ($r = -0.24$; $p = 0.03$). However, no significant correlation was found between adiponectin and HDM-specific IgE ($r = -0.21$, $p = 0.06$). In conclusion, our study reveals significant associations between adipokine levels, physical activity patterns, and the severity of allergic rhinitis (AR) symptoms in atopic individuals. Correlations between adipokine levels, symptom severity scores, and BMI further underscore the complex interplay between adiposity, physical activity, and allergic inflammation. These findings emphasize the importance of further research into personalized lifestyle interventions aimed at managing AR symptoms effectively, potentially incorporating targeted physical activity interventions.

Keywords: allergic rhinitis, atopy, physical activity, sedentary behaviour, adipokines, BMI.

1. Introduction

Allergic rhinitis (AR) represents a prevalent condition known to significantly impact the quality-of-life of affected individuals. Its hallmark symptoms encompass sneezing, nasal congestion, itching, and nasal secretion, all triggered by the presence of specific-IgE antibodies reacting to airborne allergens, including house dust mites (HDM), pet hair, and grass pollens [1,2]. Atopic individuals, characterized by a genetic predisposition to produce specific-IgE antibodies, typically exhibit a Th2 cytokine profile dominated by interleukin-4 (IL-4) and interleukin-13 (IL-13). Atopic patients also present positive results in skin prick tests (SPT), reflecting their heightened immune sensitivity to allergens [3,4]. Conversely, non-atopic individuals may manifest AR symptoms, but do not demonstrate reactivity in SPT and lack detectable levels of specific-IgE antibodies. However, the initiation of symptoms can also stem from the release of alarmins, (TSLP), such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, by stimulated or damaged epithelial cells. These alarmins play a pivotal role in exacerbating local inflammation and contribute to the pathophysiology of allergic rhinitis, a phenomenon observed similarly in asthma [5,6]. The ARIA (Allergic Rhinitis and its Impact on Asthma) recommendations categorize symptom severity into mild or moderate to severe based on factors such as the impact on sleep quality, impairment of daily or occupational activities, and the duration and discomfort associated with symptoms [7].

Individuals with AR have many risk factors that may influence the disease progression, including genetic predisposition, exposure to environmental pollutants and allergens, and emerging evidence suggests a potential role of physical activity (PA) [8]. Regular engagement in vigorous exercise has been associated with exacerbating symptoms in RA patients. Conversely, studies propose that moderate intensity activities, such as aquatic exercises, treadmill workouts, and yoga could mitigate inflammation by modulating levels of pro-inflammatory cytokines and improving lung function [9,10].

In this context, physical activity (PA) demonstrated an inverse correlation with sedentary behavior, a factor known to predispose individuals to obesity and subsequently

increase the susceptibility to allergic disorders [11,12]. Obesity triggers inflammatory processes that induce dysfunctional changes in the immune system, prompting adipocytes to release pro-inflammatory adipokines such as leptin, which is associated with Th1 profile response and regulates satiety processes and energy metabolism. However, dysregulation of leptin leads to eosinophils stimulation and the release of various inflammatory cytokines [13]. Notably, in AR elevated leptin levels correlate with the expression of type 2 cytokines exacerbating symptoms and diminishing allergenic tolerance [14,15-17]. Intriguingly, obese individuals with RA exhibit increased levels of leptin and type 2 innate lymphoid cells (ILC2), which contributed to contribute to symptom reduction compared to non-obese counterparts with RA [18]. Conversely, adiponectin present in lower amounts in obese individuals, possesses anti-inflammatory properties by promoting the production of IL-10 while reducing levels of TNF- α and IL-6, thereby maintaining immune homeostasis. Regular physical exercise is associated with elevated adiponectin levels, indicating its potential role in modulating inflammation [19]. Nevertheless, during the grass pollen exposure in seasonal allergic rhinitis, adiponectin had an inflammatory effect that exacerbated symptoms in affected individuals [20,21]. Nevertheless, during grass pollen exposure in seasonal allergic rhinitis, adiponectin exhibits an inflammatory effect, exacerbating symptoms in affected individuals [20,21]. Furthermore, resistin secreted by adipose tissue cells, has acts via a pro-inflammatory mechanism, with increased expression observed in endothelial cells, particularly in obese individuals. In AR, resistin serve as a marker of severity, contributing to allergic nasal inflammation and exacerbating moderate to severe symptoms [22,23].

Considering the significant contribution of adipokines have to inflammation in both obesity and allergy disorders, the relationship between atopy, adipokines and the impact of physical activity in this context remains elusive. Understanding the production of adipokines concerning the severity of AR symptoms and HDM-specific IgE production could shed light on the potential modulation of adipokines by physical activity in individuals with AR.

2. Material and methods

2.1. Study design

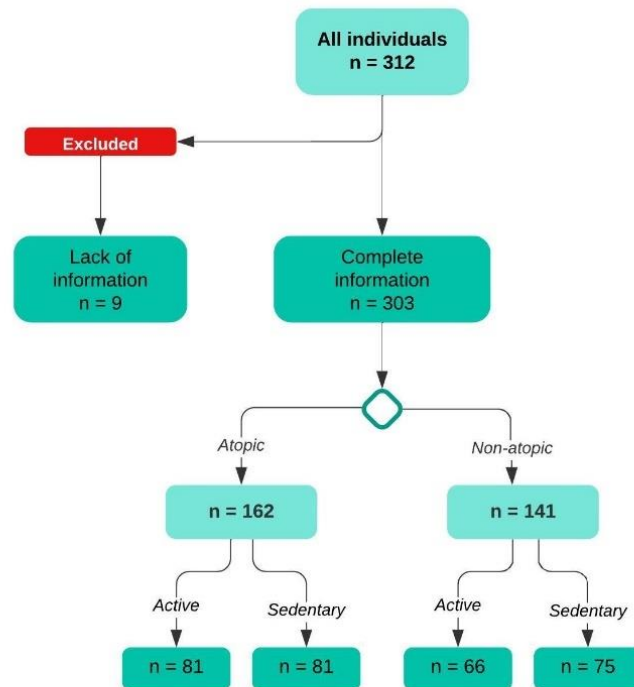


Figure 1. Study design.

The study sample included a total of 303 participants recruited at the University Hospital, Uberlândia, Brazil, with age ranging from 18 to 60 years. Atopy was determined by SPT results and/or specific-IgE levels, by ELISA. The total of 162 individuals with atopy were included in the atopic group (AT), including 81 with physical activity (PA) and 81 with sedentary behavior (SB). The 141 individuals without atopy were included in the non-atopic group (NAT), whereas 66 individuals with PA and 75 individuals with SB. The inclusion criteria were based on adult participant, irrespective of their engagement in physical activity, have atopy or non-atopic with clinical history of allergic rhinitis. Exclusion criteria included participants below 18 or above 60 years, individuals in treatment with antihistamine or corticosteroids and pregnant women. The study received approval from the Ethics Committee for Human Research at the Federal

University of Uberlândia under protocol number 4.880.402. All participants provided their signed Informed Consent Form before participating in the study.

2.2. Rhinitis questionnaire

The RCAT (Rhinitis Control Assessment Test) is a validated questionnaire to evaluate allergic rhinitis symptoms, including six questions with five answer levels, with a score outcome. The questions refer to the previous week and address main symptoms, such as nasal congestion, sneezing, and eye tearing, as well as the individual's personal opinion on how to control these symptoms [24]. The Brazilian version was adopted in this study [25]. An index (RCAT score) for each question was determined from 1 to 5 points according to the frequency of reporting, with score 5 for “never,” 4 for “rarely,” 3 for “sometimes,” 2 for “often,” and 1 for “very often”. The final RCAT score according to the total score obtained, patients were divided into two groups according to the original questionnaire validation: controlled, individuals with mild symptoms (≥ 22 points), and uncontrolled, individuals with moderate-severe symptoms (< 22 points).

2.3. SPT and HDM-specific IgE ELISA

SPT was conducted using house dust mite - HDM (*Dermatophagoides farinae*, *D. pteronyssinus*, and *Blomia tropicalis*), dog (*Canis familiaris*), and cat dander (*Felis catus*) allergen extracts (FDA Allergenic, Rio de Janeiro, Brazil) [26]. After asepsis, a drop of allergen extract was applied next to each mark. A lancet was used to prick the extracts into the skin's surface. A new lancet was used for each allergen. A wheal diameter ≥ 3 mm after 15 min was considered positive. Serum samples were used to detect HDM-specific IgE by an indirect ELISA [27]. Briefly, high-affinity microplates were coated with 40 $\mu\text{g/mL}$ of in house HDM extract for 18 h at 4°C and blocked with phosphate-buffered saline/0.05% Tween (PBS-T) with 1% Bovine Serum Albumin (BSA). Serum samples (1:2) were diluted in PBS-T-BSA and incubated at 37 °C for 2 h, followed by incubation with biotinylated anti-human IgE (Sigma-Aldrich) and streptavidin–peroxidase conjugate (ThermoFisher) (1:1000) at room temperature. The reaction was developed by adding 0.01M 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (Sigma-Aldrich) and the absorbance values were determined at 405 nm. The results were

expressed as ELISA index (EI) score, as described elsewhere [28]. $EI \geq 1.2$ was considered positive.

2.4. Physical activity/sedentary behavior classification

To investigate the level of physical activity, International Physical Activity Questionnaire (IPAQ) - Long form was carried by assessing amount of time spent engaging in various activities, including work-related tasks, household chores, pet care, type of transportation for commuting, engagement in leisure physical activities, and time spent sitting. In the anthropometric evaluation, body mass (in kilograms) and height values were obtained for the calculation of the body mass index (BMI), which is a measure used as a general indicator to assess whether an individual has a healthy body weight relative to his height. For the calculation of BMI using the formula kg/m^2 , weight, height, and age were collected for result evaluation and classification: normal (18.5-25), Overweight (25-30) and Obese (30-40). The International Physical Activity Questionnaire (IPAQ) also features classifications calculated based on reported daily physical activity levels: low (sedentary behavior); moderate and high (physical activity). To assess body muscle strength, was carried out handgrip test (Saehan "SH5001" Hand Dynamometer) that evaluated the force dominant and non-dominant arms. The mean of both arms was recorded, and the result used to calculate the index FBMI that is determined by ratio of force and BMI, with force being determined by strength testing in kg/f and BMI being determined by body mass and height (in kg/m^2). This statistic provides a more thorough assessment of total strength by including differences in body type that may introduce bias into the study. Greater force levels are correlated with higher FBMI values.

2.5. Adipokine levels

To quantification the adipokines, such as adiponectin, leptin and resistin were quantified using specific kits (R&D Systems, San Diego, USA) by ELISA following the protocol provided by the manufacturer. Briefly, high protein affinity ELISA plates were coated with specific monoclonal antibodies to capture (100 μL) and incubated for 12-16hs at 4°C. After the plates were washed three times with PBS/Tween 0,05% and locked for 4hs at room temperature with 200 μL of BSA PBS 1%. Serum samples were diluted and added (100 μL) for incubation for 18h

at 4°C with dilution of adiponectin: 1/2000; leptin: 1/50 and resistin: 1/25. After washing, the biotinylated detection secondary antibody was added and incubated for another 3 h at room temperature. The plates were washed again and incubated with a streptavidin conjugated to peroxidase (1.25 ng/mL), for 60 min at 37°C. After cycles of washing, tetramethylbenzidine (TMB) was added for reaction development and stopped with 2% H₂SO₄ after 10 minutes. Absorbance was measured at a wavelength of 450 nm using Enspire Multimode Plate Reader. Comparing the samples with a standard curve based on corresponding recombinant proteins used in specific serial dilutions was the method used to estimate their concentration.

2.6. Statistical Analysis

The statistical significance of differences based on age, IgE levels, BMI, symptoms and SPT results were assessed using Student *t*-test. Differences in sex and IPAQ answers were assessed by Fisher's exact test. Difference among adipokines, IgE, and RCAT score in atopic and non-atopic individuals were compared using Mann-Whitney test. Correlations were analyzed by Spearman Test. The value of $p < 0.05$ considered to be statistically significant. All statistical analyses were conducted using Prism 9.4 (GraphPad, Boston, MA, USA).

3. Results

3.1. Participants

Participants were invited to join the study and 303 individuals met the inclusion criteria, with 53.5% ($n = 162$) being atopic (AT) and 46.5% ($n = 141$) non-atopic (NAT) (Table 1). The majority were female in both AT (62.9%) and NAT (74.4%) groups (Table 1). Atopic patients had a median age of 30.7 years, while non-atopic individuals had a median age of 34.8 years (Table 1). The International Physical Activity Questionnaire (IPAQ) indicated that 81 (50%) people in the AT group were physically active (PA) and 81 (50%) had sedentary behaviour (SB). On the other hand, the NAT group had 66 (46.8%) PA individuals and 75 (53.2%) SB individuals (Table 1). The mean of BMI in atopic individuals was 25.6 kg/m² and non-atopic individuals was 27 kg/m². As expected, individuals from AT group had more HDM specific-IgE compared to NAT (Table 1; Figure 2A). Our analysis also focused on detecting antibody distinctions between SB and PA individuals in AT (Figure 1B) and NAT groups (Figure 2C).

However, no differences were observed in the median levels of anti-HDM IgE production in any of the groups (Figure 2B, 2C).

Table 1. Demographic and clinical features atopic (AT) and non-atopic (NAT) individuals, determined according to history and diagnosis of atopy.

Characteristic	Atopic (AT)	Non-atopic (NAT)	<i>p</i>
Individuals, n (%)	162 (53.5%)	141 (46.5%)	
Female, n (%)	102 (62.9%)	105 (74.4%)	0.0357*
Male, n (%)	60 (37.0%)	36 (25.5%)	
Age (years; mean ¹)	30.7±10.9	34.8±13.6	0.0161*
*BMI (kg/m ² ; mean ¹)	25.6±5.7	27.0±6.2	0.0637
Physical activity n (%)	81 (50%)	66 (46.8%)	0.6450
Sedentary behavior n (%)	81(50%)	75 (53.1%)	
Rhinitis mild symptoms	43 (26.5%)	6 (4.2%)	0.0001*
Rhinitis moderate-several symptoms	122 (75.3%)	136 (96.4%)	0.0001*
HDM specific-IgE (IE)	2.4±1.8	0.6±0.2	0.0001
SPT wheal size (mm; mean ¹)	5.5±3.0	0.0±0.6	0.0001

¹ mean ± standard deviation; * Body mass index; Skin Prick Test; House dust mite; Index ELISA

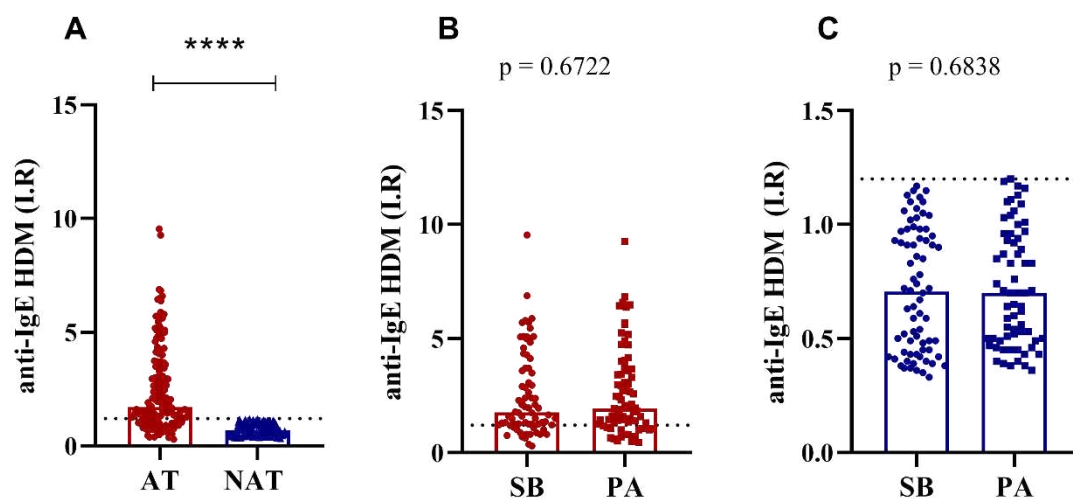


Figure 2. Levels of HDM specific-IgE in (A) both AT and NAT groups; (B) individuals with sedentary behavior (SB) and physical activity (PA) in AT group; (C) SB and PA in NAT group.

**** $p < 0.0001$. Mann Whitney test with significant considered $p < 0.05$.

3.2. Adipokines levels in AT and NAT groups

To assess potential differences between atopic and non-atopic individuals regarding adipokine behavior, we compared the levels of leptin, resistin, and adiponectin between AT and NAT two groups. Interestingly, NAT individuals had higher serum leptin levels than atopic patients (Figure 3A), although one individual had produced leptin with higher amount, compared to those in AT group. No statistically significant differences were observed in the other adipokines, although both groups produced lower amount (Figures 3B and 3C).

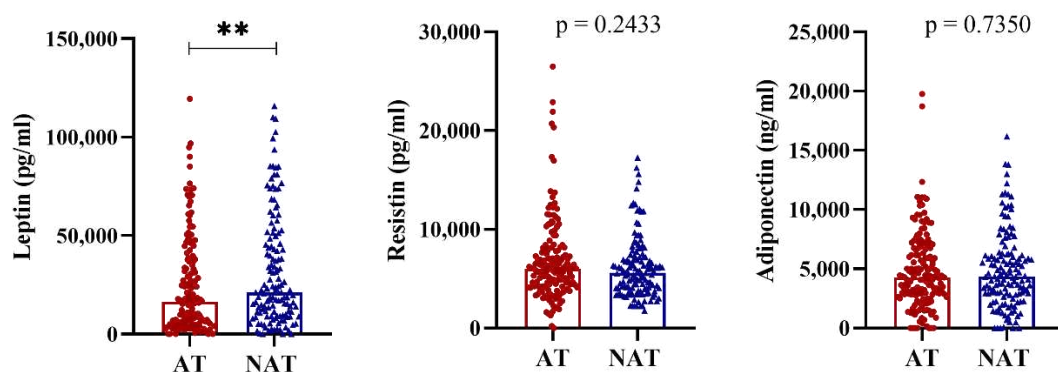


Figure 3. Comparison of serum levels of (A) leptin, (B) resistin, and (C) adiponectin between in atopic (AT) and non-atopic (NAT) groups. Statistical significance indicated by. ** $p < 0.001$.

3.3. Adipokine levels in PA and SB

To precisely determine whether atopy had an impact on adipokine levels, we separately analyzed PA and SB groups among AT and NAT individuals. SB/NAT individuals were found to have higher leptin levels (Figure 4D). However, among the PA/NAT individuals, there was no statistical difference between the groups (Figures 4A) although two individuals showed high levels, in comparison AT group irrelevant the levels of activity suggesting that atopy influences leptin levels. Surprisingly, resistin levels were significantly higher in AT/SB patients than in SB/NAT individuals, despite six individuals produce low this the adipokine (Figure 4E).

PA/AT individuals showed no difference in resistin levels, suggesting that exercise is the cause of the reduction in resistin levels (Figures 4B). SB and PA individuals, whether AT or NAT, did not show any difference in adiponectin levels (Figures 4F, 4C), even if have more scattering among individuals therefore high or low producing.

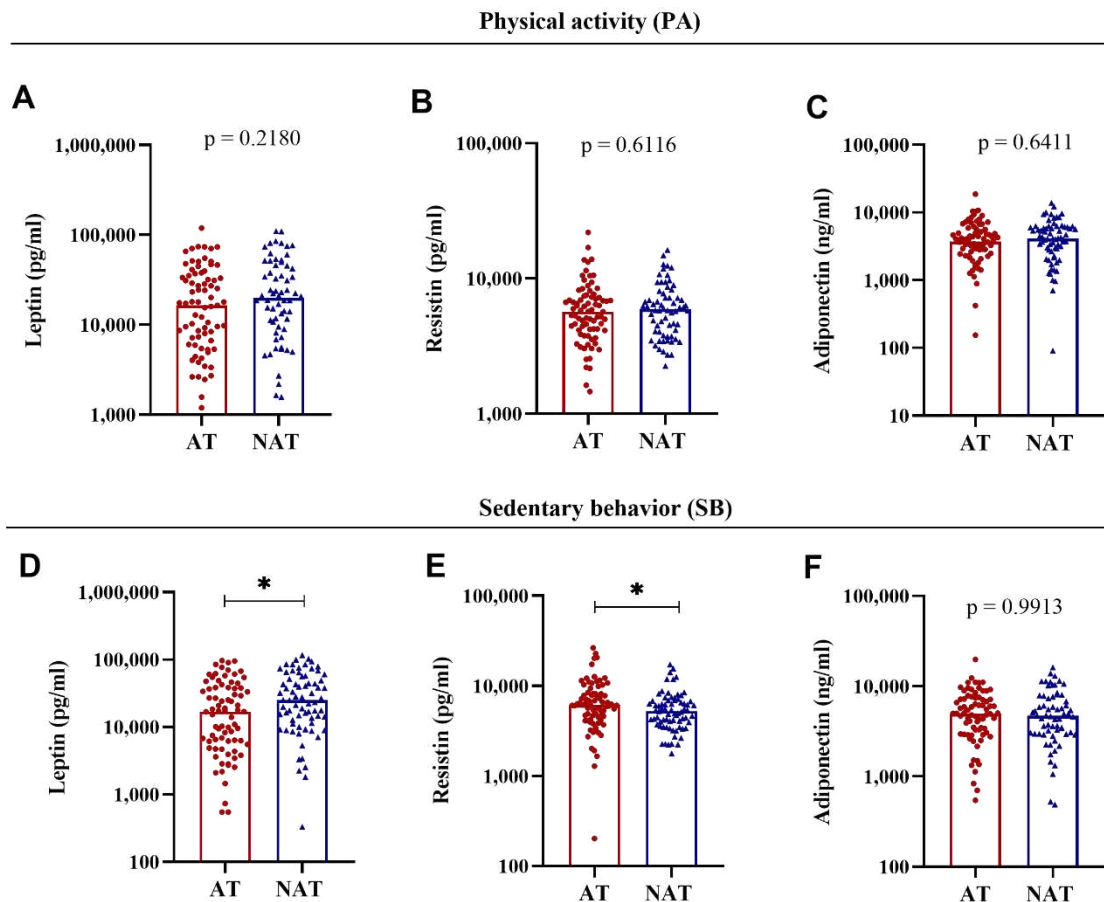


Figure 4. Comparison of adipokine levels in atopic (AT) and non-atopic (NAT) groups categorized by sedentary behavior (SB) or physical activity (PA). (A) Levels of leptin (B), resistin, and (C) adiponectin in individuals with physical activity (PA); (D) leptin, (E) resistin, and (F) adiponectin in individuals with sedentary behavior (SB). Mann Whitney test with significance indicated by * $p < 0.05$.

To determine whether physical exercise had a real effect on serum adipokine levels in the AT group, we compared SB and PA individuals. Thus, higher serum levels of adiponectin were observed in PA individuals than in SB (Figure 5C), highlighting the ability of exercise to modify the levels of this adipokine, even in AT patients, despite one individual each the group

showed high levels. However, no statistically significant differences were observed in the levels of leptin (Figure 5A), although one individual had level higher than 100,000 in PA group. Regarding resistin (Figure 5B), the same was demonstrated although five individuals reached levels higher than 15,000 in the SB group, followed by two individuals in PA group. These adipokines were also examined in PA and SB non-atopic patients, however, we did not detect any statistical differences between.

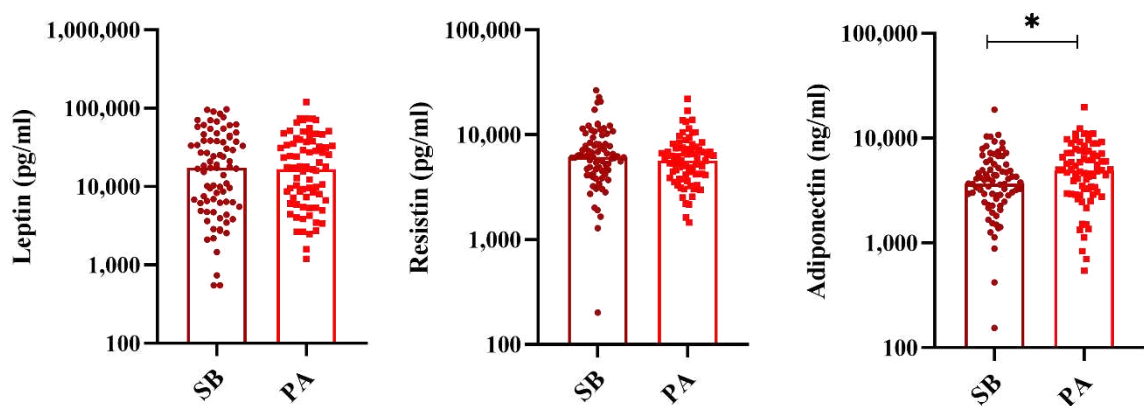


Figure 5. Comparison of adipokine levels in individuals with sedentary behavior (SB) or physical activity (PA) within the atopic (AT) group. Levels of (A) leptin (B), resistin, and (C) adiponectin. Statistical significance indicated by * $p < 0.05$.

3.4. Adipokine levels between PA and SB atopic individuals

Moreover, we found that AT/PA individuals had low-score indicated mild symptoms than AT/SB individuals that had high-score representing fewer mild symptoms number, with a statistically significant difference between the two groups (Figure 6A). Because of the variations in adipokines found among AT individuals and the smaller number of symptoms in SB individuals, we sought to assess whether the serum levels of these cytokines varied between patients with mild or severe symptoms. When comparing AT/PA patients with mild symptoms to those with severe symptoms, it was not possible to observe differences in serum adipokines levels (Figures 6B, 6C, 6D). However, we have found that AT/SB patients with severe symptoms have higher adiponectin levels when compared to those with mild symptoms, though one individual with high levels (Figure 6G). Regarding the serum levels of leptin (Figure 6E) and resistin (Figure 6F) in atopic individuals with mild and severe symptoms, no statistical

difference was observed, despite four individuals that have mild symptoms showed high levels of resistin.

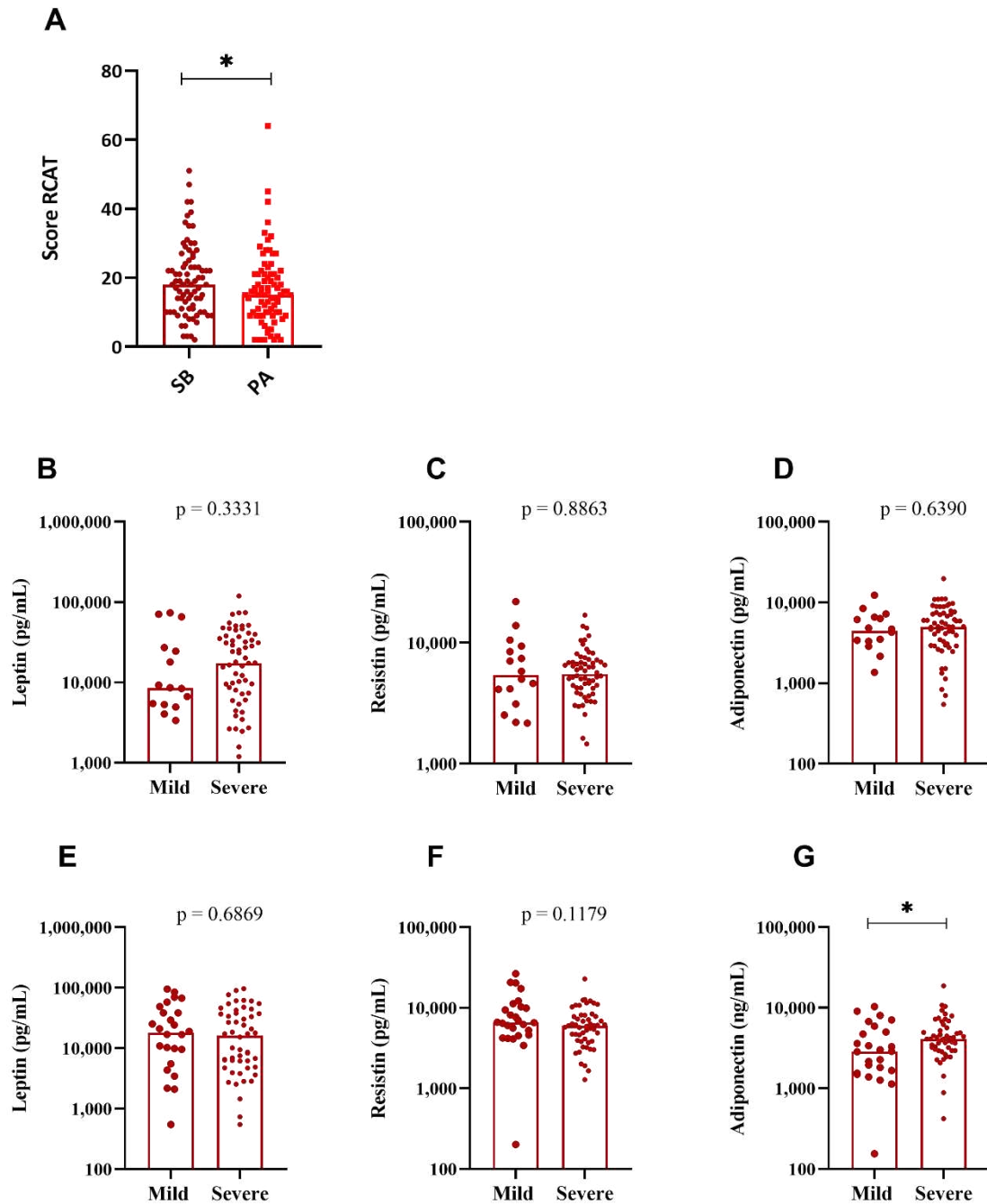


Figure 6. Comparison of RCAT scores and adipokines levels between sedentary behavior (SB) and physical activity (PA) groups within the atopic (AT) group. (A) RCAT scores among SB and PA atopic

group (B) Leptin (C) Resistin (D) Adiponectin levels in AT/PA subgroups with mild and severe symptoms (E) Leptin (F) Resistin (G) Adiponectin levels in AT/SB subgroups with mild and severe symptoms. Statistical significance indicated by * $p < 0.05$.

3.5. Adipokines and BMI in AT and NAT

We aimed to determine if the differences in serum adipokine levels were influenced by body mass index (BMI). The levels of these cytokines were compared between the groups with adequate body weight and those who were obese. AT obese individuals had higher serum leptin levels than those with AT non-obese weight (Figure 7A). However, there were no differences in the serum levels of resistin (Figure 7B) and adiponectin (Figure 7C). Furthermore, we assessed whether serum adipokine levels differed between individuals non-obese and obese individuals in the atopic and non-atopic groups. However, our analyses did not show statistically significant differences when the groups were analyzed separately (data not shown), indicating that the previously observed differences within the atopic group were not due to BMI.

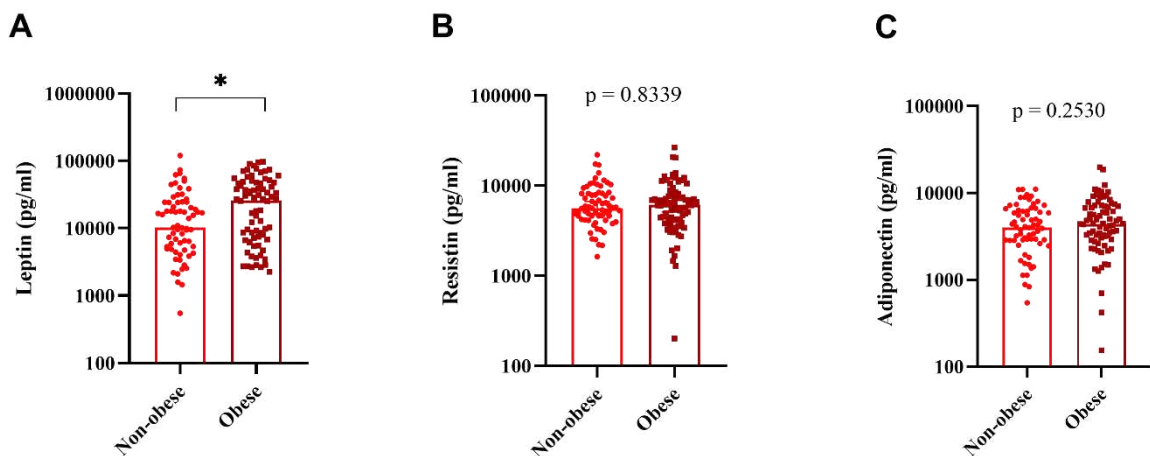


Figure 7. Comparison of adipokines levels in the atopic (AT) group based on body mass index (BMI). (A) Levels of leptin (B) Resistin (C) Adiponectin between non-obese and obese subgroups within AT group. Statistical significance indicated by * $p < 0.05$.

3.6. Correlations among variables in general groups (AT and NAT), sedentary behavior and physical activity

Firstly, the analyses were conducted to investigate correlations among the study variables in both groups AT and NAT irrelevant levels of activity. The HDM-specific IgE and score of RA were positively correlated ($r = 0.48$, $p < 0.0001$). In addition, there was a slight but negative correlation between score and adiponectin in the serum ($r = -0.18$, $p = 0.02$), whereas serum leptin levels and BMI were positivity correlated ($r = 0.22$; $p = 0.007$), meanwhile leptin levels and FBMI were negativity correlated ($r = -0.32$, $p < 0.0001$), indicated that BMI not real BMI showed a negative correlation with BMI ($r = -0.46$), indicating that the FIMC can be used as a parameter for assessing activity levels (Figure 8C).

For correlation among AT and NAT groups, data were assessed in PA and SB groups (Figure 8A, 8B). The PA group expressed negative correlation between leptin levels and score RCAT ($r = -0.26$, $p = 0.02$). The adiponectin and resistin levels were positivity correlated ($r = 0.33$, $p = 0.03$) (Figure 8A). Nevertheless, in the SB group observed slight positivity correlation between score and resistin levels. The adiponectin levels were negativity correlated with score of RA, although IgE levels not correlated with adiponectin ($r = -0.21$, $p = 0.06$) and resistin levels ($r = 0.19$, $p = 0.08$). In relation to BMI, was slight correlated positivity with leptin levels ($r = 0.26$, $p = 0.02$), but FBMI and leptin was moderate correlated negativity among them ($r = -0.46$, $p < 0.0001$). That way, BMI and FBMI moderate negatively correlated each other ($r = -0.54$, $p < 0.0001$) (Figure 8B).

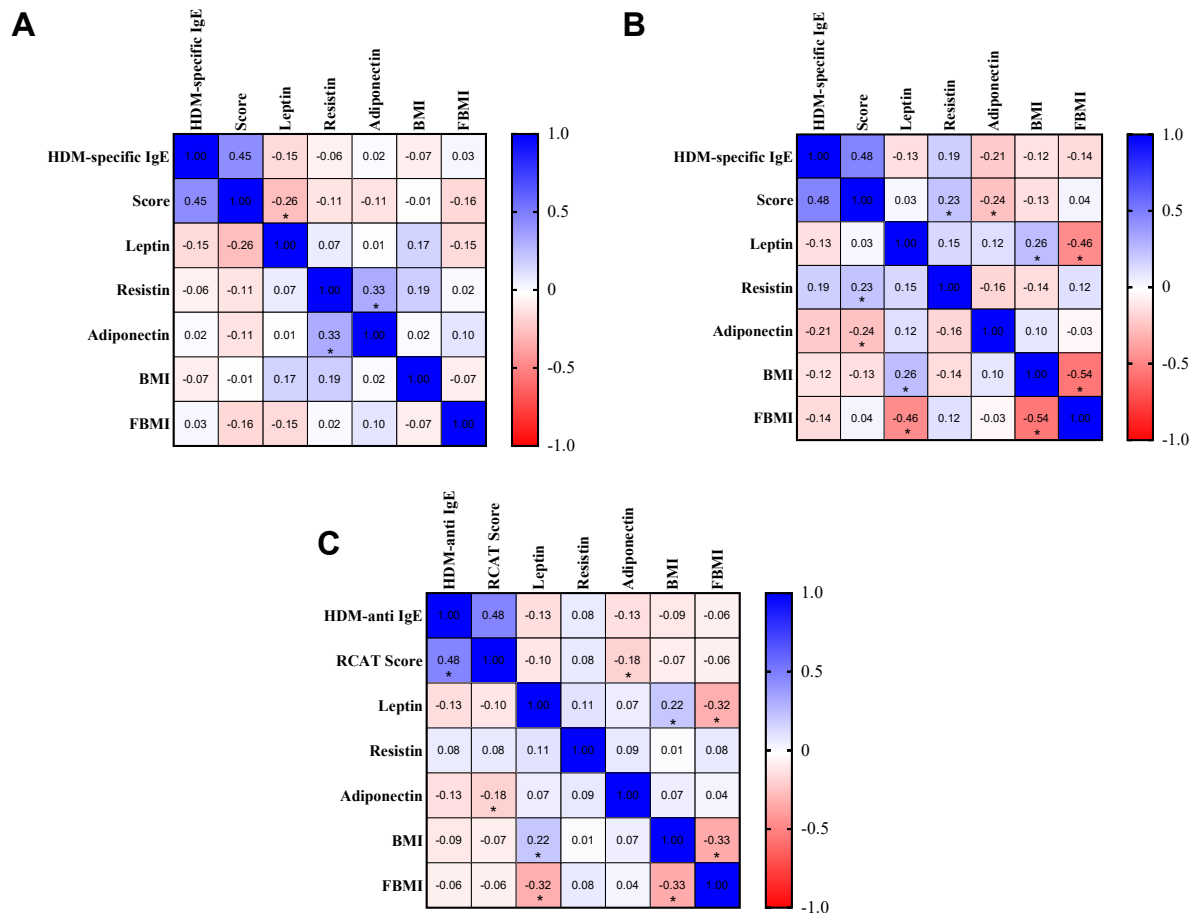


Figure 8. Correlation profile among adipokines, RCAT score, and body/immunological parameters.

(A) Physical activity (PA) (B) Sedentary behavior (SB) (C) Atopic (AT) and non-atopic (NAT) groups. Statistical significance indicated by * $p < 0.05$.

4. Discussion

The current study aimed to assess the modulation of different adipokine profiles (leptin, resistin, and adiponectin) related to the presence or absence of IgE and allergic rhinitis (AR) symptoms, as well as physical activity or sedentary behavior. Participants were categorized into atopic (AT) and non-atopic (NAT) groups based on their SPT and HDM-specific IgE outcomes. Among the atopic population, elevated levels of HDM-specific IgE were detected, with all participants testing positive on SPT and experiencing symptoms of AR ranging from mild to severe. These findings are consistent with previous studies demonstrating that positive SPT and allergen-specific IgE are reliable indicators for diagnosing allergen sensitization, particularly

for assessing allergenic groups within mite species such as *Dermatophagoides pteronyssinus*, including Der p 5 to Der p 21 allergens, which are commonly associated with respiratory allergies [29,30]. Regarding the level of physical activity, half of the individuals with atopic conditions were engaged in physical activity, while the other half were sedentary. This balanced distribution is typically uncommon, as individuals with respiratory diseases often to avoid physical activity due to discomfort or the inability to control symptoms, particularly among those who have asthma [31].

Specific IgE may directly correlate with the symptoms of AR, as we have found. However, the presence of symptoms is not always indicative of atopy. In our study, all individuals with atopy reported respiratory symptoms suggestive of AR. The symptoms of AR and asthma are caused by inhalant allergens that trigger both local and systemic responses through inflammatory immune reactions mediated by IgE or other components, such as alarmins, IgG, and complement activation [32]. In NAT, it is likely that individuals experienced AR symptoms that were not driven by specific IgE.

Atopic individuals may exhibit an exacerbated immune response profile, however, several studies have demonstrated the importance of regular physical exercise in alleviating allergy symptoms, with the intensity of the activity playing a pivotal role in clinical management [33]. Moreover, there is a no concern regarding the production of adipokines in individuals diagnosed with AR and allergies [34], a phenomenon also observed among those with sedentary behavior and in overweight or obese individuals with comorbidities and who are often evaluated during physical activity interventions [35].

In the current investigation, AT individuals displayed decreased leptin levels in contrast to their NAT counterparts, aligning with prior studies that has delineated heightened levels of leptin among allergic individuals with AR when compared to non-allergic counterparts, irrespective of atopy and asthma comorbidity [36,37]. Notably, researchers have documented increased levels of both leptin and adiponectin in individuals with AR, with a concomitant association with heightened symptom severity [38]. However, in the scope of our study, no discernible variance in adiponectin levels was noted between AT and NAT individuals diagnosed with AR. Against this backdrop, our investigation aimed to elucidate the potential impact of physical activity and sedentary lifestyle on adipokines profiles within these cohorts.

Our findings reveal that physically active AT individuals exhibit a more pronounced elevation in adiponectin levels relative to their sedentary counterparts, a trend consistent with previous findings demonstrating heightened adiponectin levels in individuals engaged in regular physical exercise [39]. Adiponectin, recognized as an anti-inflammatory cytokine in this context, although subject to conflicting interpretations in the realm of allergic conditions [40], showcases an inverse correlation with symptom severity in the sedentary AT group, albeit not with IgE levels, thus echoing conclusions drawn from earlier investigations.

The discernible absence of significant disparity in leptin levels between individuals with AT and NAT, regardless of their engagement in SB or PA, hints at a potential linkage between the observed decrease in leptin within the AT group compared to NAT and underlying immunological processes of type 2 response characteristic of atopy. Notably, leptin predominantly exhibits a polarization for the induction of Th1 immune responses, inducing TNF- α and IFN- γ production, thereby promoting suppression of Th2-mediated immune responses [41]. However, experimental models have indicated that leptin deficiency was associated with decreased polarization of both Th1 and Th2 responses, resulting in diminished levels of IFN- γ and IL-4 cytokines, respectively, particularly in Th2-dependent inflammatory conditions such as colitis, thereby affording a protective effect against inflammation driven by Th2 responses, thus highlighting its regulatory potential in such immunological milieu [42].

Within the PA cohort, a notable inverse correlation emerges between leptin levels and with the severity of rhinitis symptoms. However, while studies demonstrate benefits and the protective effect of physical exercise in asthmatic individuals [43], scenario differs in AR, where vigorous exercises are associated with exacerbated symptoms and increased levels of IgE specific to aeroallergens. Consequently, the precise role of leptin within this group, particularly in the context of allergic diseases and atopy, warrants more comprehensive investigation [9].

Regarding symptoms, we assessed if adipokines in AT and NAT subjects both SB and PA could affect symptom severity. Our evaluation showed that AT/SB individuals had a lower symptom score compared to the AT/PA group. Studies suggest that exercise-induced rhinitis (RIE), which mostly occurs during exercise that requires deep breathing and allows the easy entry of allergens triggering symptoms and inflammation due to the accumulation of particles

in the nasal region, may be the cause of the increase in symptoms in athletes with RA. People who are predisposed to RIE may also be affected by changes in the morphology of their nasal vestibule, which can affect how air enters and exits the lungs [44].

In our present investigation, we did not assess the physical performance of individuals; however, our analysis revealed that the AT/SB subgroup exhibited a diminished symptom score in comparison to their counterparts in the PA cohort. In this context, adiponectin levels were higher in those who had severe symptoms, with some individuals presenting mild symptoms. These findings align with studies reporting increased levels of adiponectin in symptomatic AR patients, suggesting a potential correlation with symptom severity and contributing to dysfunction in the nasal allergic mucosa [38,45,46]. Nonetheless, there was a negative correlation between adiponectin levels and symptom score, with studies indicating that its deficiency may exacerbate allergic inflammation and pulmonary remodeling [47].

The results indicated that atopic obese individuals have higher levels of leptin than non-AT obese counterparts. These findings are consistent with studies conducted in obese and AR patients, as leptin production induces IL-17 and increased ILC2s cells, which contribute to inflammation and exacerbation of symptoms. Adipokine levels were observed in both obese and non-obese AT patients based on their BMI [18,48]. In addition, while demonstrating gender differences, leptin and BMI levels positively correlated in the SB group, with other research yielding similar outcomes, particularly regarding higher levels in women with elevated BMI. Conversely, research has indicated an inverse correlation between FBMI and leptin, meaning that higher index values correspond to healthier and more active individuals with lower leptin levels. In this regard, exercise and a restricted diet have been demonstrated to lower leptin levels [49].

5. Conclusion

This study proposes valuable insights into the modulation of adipokine profiles (leptin, resistin, and adiponectin) concerning IgE levels and allergic rhinitis (AR) symptoms, while also considering the influence of physical activity and sedentary behavior. The findings highlight the importance of considering lifestyle factors, such as physical activity and sedentary behavior,

in the management of allergic rhinitis. They suggest that interventions aimed at modulating adipokine levels through lifestyle changes could potentially alleviate symptoms in atopic individuals. However, further studies are warranted to elucidate the mechanisms underlying these relationships and to explore potential therapeutic strategies that integrate lifestyle modifications for the effective management of AR and related allergic conditions.

Disclosure statement

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Data availability statement

The authors will provide access to the raw data that backs up the conclusions of this article upon request.

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5. Considerações finais

5.1. Contribuições para a saúde pública

Os achados deste estudo proporcionaram uma visão holística de questões cruciais relacionadas à vacinação contra a COVID-19, avaliação da imunidade humoral e influência da atividade física, comportamento sedentário e modulação de adipocinas em indivíduos com alergia respiratória, particularmente a rinite alérgica. Coletivamente, esses estudos oferecem *insights* abrangentes para otimizar estratégias de vacinação, aprimorar a avaliação da resposta imune e refinar abordagens terapêuticas para condições alérgicas.

O primeiro manuscrito, "*Distinct Adverse Reactions to mRNA, Inactivated Virus, and Adenovirus Vector COVID-19 Vaccines: Insights from a Cohort Study on Atopic and Non-Atopic Subjects in Brazil*", destaca a importância de considerar os perfis alérgicos individuais na administração da vacina. Ao afirmar a segurança da vacinação contra a COVID-19 em indivíduos com alergias respiratórias, o estudo chama a atenção para a necessidade de orientações personalizadas, especialmente em relação à vacina ChAdOx1, para mitigar eventos adversos leves de forma eficaz.

O segundo manuscrito, "*Prevalence of SARS-CoV-2 neutralizing antibodies in individuals vaccinated and unvaccinated for COVID-19 in Brazil using point-of-care diagnostic test*", destaca a utilidade de testes rápidos na avaliação da imunidade humoral. Este estudo enfatiza o papel crucial de tais testes na avaliação da eficácia da vacina, monitoramento da duração da imunidade e adaptação a variantes emergentes, informando efetivamente estratégias futuras de imunização.

O terceiro manuscrito, "*Adipokines and antibody response in individuals with physical activity and sedentary behavior following COVID-19 vaccination*", ofereceu uma perspectiva promissora sobre o impacto benéfico do exercício físico na resposta imune à vacinação contra a COVID-19. Além disso, destaca a influência do gênero e da atividade física nos níveis de citocinas e produção de anticorpos, ressaltando a necessidade de abordagens multifacetadas para elucidar de maneira compreensiva os mecanismos subjacentes.

Por fim, o quarto manuscrito, "*Physical activity, sedentary behavior, and adipokines production in atopic individuals with allergic rhinitis*", ressalta o potencial das modificações no estilo de vida, como a prática de atividade física na redução dos sintomas e na gestão eficaz

da alergia respiratória, incluindo a rinite alérgica. Ao elucidar a interação entre atividade física, comportamento sedentário e modulação dos perfis de adipocinas em relação à gravidade dos sintomas e aos níveis de anticorpos IgE, o estudo forneceu insights valiosos, como a produção de adipocinas em indivíduos atópicos, que são moduladas de acordo com o comportamento em relação a atividade física. Isso esclarece o mecanismo da resposta imune, sendo o exercício uma estratégia terapêutica promissora e integrativa na melhora dos sintomas de alergias respiratórias.

Globalmente, esses estudos contribuem significativamente para o avanço do conhecimento em saúde pública, fornecendo uma base sólida para o desenvolvimento de estratégias mais direcionadas e eficazes para a vacinação contra a COVID-19, monitoramento da imunidade humoral e gestão de condições alérgicas. Essas descobertas têm o potencial de apontar o caminho para estratégias de políticas de saúde e práticas clínicas, visando melhorar a saúde e o bem-estar da população.

5.2. Conclusões finais

A) Atopia e perfil de segurança das vacinas de COVID-19

- Indivíduos atópicos apresentam maior incidência de efeitos adversos após administração da vacina ChAdOx1 em comparação aos não atópicos;
- É necessário orientar a população atópica sobre possíveis efeitos adversos associados à vacinação contra a COVID-19;
- Os profissionais de saúde devem considerar os benefícios e riscos potenciais de cada vacina com base no histórico do paciente antes de decidir pela sua administração.

B) Correlato de imunidade e vacinas para COVID-19

- O teste rápido demonstra eficácia na identificação de NAbs durante a infecção do SARS-CoV-2 e após-vacinação com diferentes plataformas vacinais;

-
- A plataforma LFIA na detecção de NAbs desempenha um papel importante na epidemiologia da COVID-19 principalmente devido à sua capacidade de identificação rápida em indivíduos após a vacinação.

C) Exercícios físicos como adjuvantes em vacinas para COVID-19

- O exercício físico demonstrou influenciar a resposta imune desencadeada pela vacinação contra COVID-19;
- A produção de adipocinas parece estar intimamente relacionada à proteção após conferida pela vacinação;
- O índice FIMC se mostra uma importante ferramenta na distinção entre indivíduos ativos e sedentários;
- Mulheres exibem maior produção de anticorpos após a vacinação.

D) Exercícios físicos na alergia respiratória

- O exercício físico foi capaz de modular as respostas imunológicas em indivíduos atópicos;
- O exercício físico contribui para a redução do escore de gravidade dos sintomas de rinite alérgica em indivíduos atópicos;
- A produção de adipocinas parece apresentar uma correlação estreita com a gravidade dos sintomas de rinite alérgica e atopia.

ANEXO 1
QUESTIONÁRIO PARA AVALIAÇÃO DE RESPOSTA IMUNE APÓS VACINA
CONTRA COVID-19

1. Código: _____
2. Profissão: _____
3. Data de nascimento: ____/____/____
4. Gênero: () Feminino () Masculino
5. Teve COVID-19? () Sim () Não () Não sei
 Se sim, quando? _____
 Foi internado e/ou intubado? () Sim () Não
6. Você teve sintomas que persistiram após a doença (pós-Covid)?
 () Sim () Não
Se sim, quais? (verificar lista questionário online**)
-

- Por quanto tempo? _____ meses
7. Tem algum exame sorológico positivo para IgM ou IgG contra COVID-19?
 () Sim () Não () Não sei
8. Possui alguma doença/condição abaixo?
 () Hipertensão () DPOC () Diabetes () Câncer () Tabagismo
 () Obesidade () Gestante () Puérpera () Síndrome de Down
 () Renal Crônico
 Outro, qual? _____
9. Faz uso de medicamentos de forma crônica? () Sim () Não
Se sim, quais? _____
10. Faz uso de suplementos alimentares? () Sim () Não
Se sim, qual(is): _____
11. Você considera sua alimentação saudável (com o consumo regular de frutas, verduras, alimentos naturais, carnes e menos processados)?
 () Sim () Não
12. Com relação à vacinação para COVID-19, preencha os campos abaixo:
 a) Primeira dose (ou dose única):
Data: ____/____/____ Cidade/Estado: _____
() 1. AstraZeneca/Fiocruz
() 2. Sinovac/Butantan
() 3. Pfizer
() 4. Janssen
() 5. Sputnik V
() 6. Outra: _____
Teve algum efeito colateral (reação adversa)? () Sim () Não
Se sim, qual (is)? _____
-
-

b) Segunda dose (quando aplicável):

Data: ____/____/____ Cidade/Estado: _____

☐ 1. AstraZeneca/Fiocruz☐ 2. Sinovac/Butantan☐ 3. Pfizer☐ 4. Janssen☐ 5. Sputnik V☐ 6. Outra: _____Teve algum efeito colateral (reação adversa)? (☐) Sim (☐) NãoSe sim, qual (is)?

c) Terceira dose (quando aplicável)

Data: ____/____/____ Cidade/Estado: _____

☐ 1. AstraZeneca/Fiocruz☐ 2. Sinovac/Butantan☐ 3. Pfizer☐ 4. Janssen☐ 5. Sputnik V☐ 6. Outra: _____Teve algum efeito colateral (reação adversa)? (☐) Sim (☐) NãoSe sim, qual (is)?

ANEXO 2
TESTE DE CONTROLE DA ASMA
Asthma Control Test (ACT)

Código do participante: _____

Nas últimas quatro semanas:

1. A asma prejudicou suas atividades no trabalho, na escola ou em casa?

- ☐ Nenhuma vez
- ☐ Poucas vezes
- ☐ Algumas vezes
- ☐ Maioria das vezes
- ☐ Todo o tempo

2. Como está o controle da sua asma?

- ☐ Totalmente descontrolada
- ☐ Pobrementemente controlada
- ☐ Um pouco controlada
- ☐ Bem controlada
- ☐ Completamente controlada

3. Quantas vezes você teve falta de ar?

- ☐ De jeito nenhum
- ☐ Uma ou duas vezes por semana
- ☐ Três a seis vezes por semana
- ☐ Uma vez ao dia
- ☐ Mais que uma vez ao dia

4. A asma acordou você à noite ou mais cedo que de costume?

- ☐ De jeito nenhum
- ☐ Uma ou duas vezes
- ☐ Uma vez por semana
- ☐ Duas ou três noites por semana
- ☐ Quatro ou mais noites por semana

5. Quantas vezes você usou o remédio por inalação para alívio?

- ☐ De jeito nenhum
- ☐ Uma vez por semana ou menos
- ☐ Poucas vezes por semana
- ☐ Uma ou duas vezes por dia
- ☐ Três ou mais vezes por dia

Fonte: ROXO et al. Validação do Teste de Controle da Asma em português para uso no Brasil. **J Bras Pneumol.** 2010;36(2):159-166

ANEXO 3
TESTE DE AVALIAÇÃO DE CONTROLE DA RINITE
Rhinitis Control Assessment Test (RCAT)

Código do participante: _____

1) Durante a última semana, com que frequência você apresentou obstrução nasal?

Nunca	Raramente	Às vezes	Frequentemente	Muito Frequente
• 5	• 4	• 3	• 2	• 1

2) Durante a última semana, com que frequência você espirrou?

Nunca	Raramente	Às vezes	Frequentemente	Muito Frequente
• 5	• 4	• 3	• 2	• 1

3) Durante a última semana, com que frequência seus olhos lacrimejaram?

Nunca	Raramente	Às vezes	Frequentemente	Muito Frequente
• 5	• 4	• 3	• 2	• 1

4) Durante a última semana, quanto seus sintomas nasais ou alérgicos interferiram com o seu sono?

Nunca	Raramente	Às vezes	Frequentemente	Muito Frequente
• 5	• 4	• 3	• 2	• 1

5) Durante a última semana, com que frequência você evitou alguma atividade (por exemplo, visitar uma casa com gato ou cachorro) devido aos seus sintomas nasais ou de outras alergias?

Nunca	Raramente	Às vezes	Frequentemente	Muito Frequente
• 5	• 4	• 3	• 2	• 1

6) Durante a última semana, quanto seus sintomas nasais ou alérgicos estiveram controlado?

Nunca	Raramente	Às vezes	Frequentemente	Muito Frequente
• 5	• 4	• 3	• 2	• 1

Fonte: Fernandes et al. Translation into Portuguese and validation of the Rhinitis Control Assessment Test (RCAT) questionnaire. Braz J Otorhinolaryngol. 2016;82(6):674-679

ANEXO 4**Questionário Internacional de Atividade Física**
International Physical Activity Questionnaire (IPAQ)

Forma longa, semana usual /normal

Código do participante: _____

As perguntas estão relacionadas ao tempo que você gasta fazendo atividade física em uma semana normal/habitual

Para responder às questões lembre-se que:

- atividades físicas vigorosas são aquelas que precisam de um grande esforço físico e que fazem respirar muito mais forte que o normal.
- atividades físicas moderadas são aquelas que precisam de algum esforço físico e que fazem respirar um pouco mais forte que o normal.
- atividades físicas leves são aquelas em que o esforço físico é normal, fazendo com que a respiração seja normal.

DAS QUESTÕES 1B a 4C O QUADRO ABAIXO DEVERÁ ESTAR DISPONÍVEL PARA PREENCHIMENTO

As próximas questões relacionam-se com toda a atividade física que você faz em uma semana normal/habitual, como parte do seu trabalho remunerado ou voluntário. Não inclua o transporte para o trabalho. Pense apenas naquelas atividades que durem pelo menos 10 minutos contínuos dentro de seu trabalho:

1b. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você realiza atividades VIGOROSAS como: trabalho de construção pesada, levantar e transportar objetos pesados, cortar lenha, serrar madeira, cortar grama, pintar casa, cavar valas ou buracos, subir escadas como parte do seu trabalho remunerado ou voluntário, por pelo menos 10 MINUTOS CONTÍNUOS?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para a questão 1c.

1c. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você realiza atividades MODERADAS, como: levantar e transportar pequenos objetos, la-var roupas com as mãos, limpar vidros, varrer ou limpar o chão, carregar crianças no colo, como parte do seu trabalho remunerado ou voluntário, por pelo menos 10 MINUTOS CONTÍNUOS?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para a questão 1d.

1d. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você CAMINHA, NO SEU TRABALHO remunerado ou voluntário por pelo menos 10 MINUTOS CONTÍNUOS? Por favor, não inclua o caminhar como forma de transpor-te para ir ou voltar do trabalho ou do local que você é voluntário.

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para a Domínio 2 -

Transporte.

DOMÍNIO 2 – ATIVIDADE FÍSICA COMO MEIO DE TRANSPORTE

DOMÍNIO 1 – ATIVIDADE FÍSICA NO TRABALHO: Este domínio inclui as atividades que você faz no seu trabalho remunerado ou voluntário, e as atividades na universidade, faculdade ou escola (trabalho intelectual). Não incluir as tarefas domésticas, cuidar do jardim e da casa ou tomar conta da sua família. Estas serão incluídas no Domínio 3.

1a. Atualmente você tem ocupação remunerada ou faz trabalho voluntário fora de sua casa?

() Sim () Não – Caso você responda não, Vá para o Domínio 2: Transporte

Estas questões se referem à forma normal como você se desloca de um lugar para outro, incluindo seu grupo de convivência para idosos, igreja, supermercado, trabalho, cinema, lojas e outros.

2a. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você ANDA DE ÔNIBUS E CARRO/MOTO?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para questão 2b.

Agora pense somente em relação a caminhar ou pedalar para ir de um lugar a outro

► em uma semana normal

► 2b. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você ANDA DE BICICLETA para ir de um lugar para outro por pelo menos 10 minutos contínuos? (Não inclua o pedalar por lazer ou exercício)

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para a questão 2d.

2c. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você CAMINHA para ir de um lugar para outro, como: ir ao grupo de convivência para idosos, igreja, supermercado, médico, banco, visita a amigo, vizinho e parentes por pelo menos 10 minutos contínuos?

(NÃO INCLUA as Caminhadas por Lazer ou Exercício Físico)

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para o Domínio 3.

DOMÍNIO 3 – ATIVIDADE FÍSICA EM CASA OU APARTAMENTO: TRABALHO, TAREFAS DOMÉSTICAS E CUIDAR DA FAMÍLIA

Esta parte inclui as atividades físicas que você faz em uma semana normal/habitual dentro e ao redor da sua casa ou apartamento. Por exemplo: trabalho doméstico, cuidar do jardim, cuidar do quintal, trabalho de manutenção da casa e para cuidar da sua família. Novamente pense somente naquelas atividades físicas com duração por pelo menos 10 minutos contínuos.

3a. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você faz Atividades Físicas VIGOROSAS AO REDOR DE SUA CASA OU APARTAMENTO (QUINTAL OU JARDIM) como: carpir, cortar lenha, serrar madeira, pintar casa, levantar e transportar objetos pesados, cortar grama, por pelo menos 10 MINUTOS CONTÍNUOS?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para a questão 3b.

3b. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você faz atividades MODERADAS AO REDOR de sua casa ou apartamento (jardim ou quintal) como: levantar e carregar pequenos objetos, limpar a garagem, serviço de jardinagem em geral, por pelo menos 10 minutos contínuos?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para questão 3c.

3c. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal você faz atividades MODERADAS DENTRO da sua casa ou apartamento como: carregar pesos leves, limpar vidros e/ou janelas, lavar roupas a mão, limpar banheiro e o chão, por pelo menos 10 minutos contínuos?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para o Domínio 4.

DOMÍNIO 4 – ATIVIDADES FÍSICAS DE RECREAÇÃO, ESPORTE, EXERCÍCIO E DE LAZER

Este domínio se refere às atividades físicas que você faz em uma semana normal/ habitual unicamente por recreação, esporte, exercício ou lazer. Novamente pense somente nas atividades físicas que você faz por pelo menos 10 minutos contínuos. Por favor não inclua atividades que você já tenha citado.

4a. Sem contar qualquer caminhada que você tenha citado anteriormente, quantos dias e qual o tempo (horas e minutos) durante uma semana normal, você CAMI-NHA (exercício físico) no seu tempo livre por PELO MENOS 10 MINUTOS CONTÍNUOS?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para questão 4c.

4b. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal, você faz atividades VIGOROSAS no seu tempo livre como: correr, nadar rápido, musculação, canoagem, remo, enfim, esportes em geral por pelo menos 10 minutos contínuos?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para questão 4d.

4c. Quantos dias e qual o tempo (horas e minutos) durante uma semana normal, você faz atividades MODERADAS no seu tempo livre como: pedalar em ritmo moderado, jogar voleibol recreativo, fazer hidroginástica, ginástica para a terceira idade, dançar... pelo menos 10 minutos contínuos?

_____ horas _____ min. _____ dias por semana () Nenhum. Vá para o Domínio 5.

DOMÍNIO 5 – TEMPO GASTO SENTADO

Estas últimas questões são sobre o tempo que você permanece sentado em diferentes locais como exemplo: em casa, no grupo de convivência para idosos, no consultório médico e outros. Isso inclui o tempo sentado, enquanto descansa, assiste a televisão, faz trabalhos manuais, visita amigos e parentes, faz leituras, telefonemas e realiza as refeições. Não inclua o tempo gasto sentado durante o transporte em ônibus, carro, trem e metrô.

5a. Quanto tempo, no total, você gasta sentado durante UM DIA de semana normal?

UM DIA _____ horas _____ minutos

5b. Quanto tempo, no total, você gasta sentado durante UM DIA de final de semana normal?

UM DIA _____ horas _____ minutos

Fonte: Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, Braggion G. QUESTIONÁRIO INTERNACIONAL DE ATIVIDADE FÍSICA (IPAQ): ESTUDO DE VALIDADE E REPRODUTIBILIDADE NO BRASIL. **Rev. Bras. Ativ. Fís. Saúde** [Internet]. 15º de outubro de 2012 [citado 14º de julho de 2021];6(2):5-18. Disponível em: <https://rbafs.org.br/RBAFS/article/view/93>.

ANEXO 5



PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Influência da alergia e do exercício físico na resposta vacinal contra SARS-CoV-2 em indivíduos vacinados para COVID-19.

Pesquisador: Ernesto Akio Taketomi

Área Temática:

Versão: 3

CAAE: 50001421.7.0000.5152

Instituição Proponente: Universidade Federal de Uberlândia/ UFU/ MG

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.959.436

Apresentação do Projeto:

Trata-se de atendimento a pendência apontadas no parecer nº 4.944.831 de 31 de agosto de 2021. As informações deste parecer foram retiradas do arquivo: PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1791027.pdf, datada 03/09/2021.

Objetivo da Pesquisa:**Objetivo Primário:**

Avaliar a influência da alergia e do exercício físico resposta imune humoral e celular após a vacinação contra COVID-19.

Objetivo Secundário:

- Determinar a presença ou ausência de doença alérgica que realizam ou não atividade física regularmente entre os indivíduos vacinados contra COVID-19;
- Determinar o nível de atividade física entre os indivíduos vacinados contra COVID-19 por meio de questionários validados e avaliações antropométricas e de força;
- Detecção de anticorpos IgM e IgG específicos dirigidos contra as proteínas S e N de SARS-CoV-2 previamente à vacinação e em cinco tempos variáveis após a primeira e segunda dose vacinal;
- Determinar a resposta imune celular a SARS-CoV-2 por meio da detecção de citocinas produzidas por células mononucleares do sangue periférico após estimulação com antígeno de



Continuação do Parecer: 4.958.436

SARS-CoV-2;

- Detecção de anticorpos IgE e IgG específicos a *Dermatophagoides pteronyssinus* e *D. farinae* no soro de indivíduos no início do estudo e realização de testes cutâneos de punção com alérgenos inaláveis 30 dias após a vacinação contra COVID-19.

Avaliação dos Riscos e Benefícios:

Riscos:

Os riscos relacionados ao estudo incluem: o constrangimento, por parte do participante, pela invasão de privacidade e pela relação com estranhos; medo pela discriminação individual ou coletiva resultante da divulgação dos resultados; interferência na rotina de trabalho do participante; possibilidade de utilização de dados para pesquisas futuras sem a devida anuência; desmaio pela coleta de sangue. Pelos pesquisadores, serão adotadas providências para evitar ou reduzir os riscos ao participante, sendo elas: garantir um local reservado e a liberdade para não responder questões julgadas como constrangedoras pelo participante; garantir que os pesquisadores estejam devidamente habilitados para a coleta dos dados; estar atento aos sinais verbais e gestuais de desconforto e constrangimento; restringir o acesso aos dados coletados; garantir a não violação e a integridade dos documentos (danos físicos, cópias e rasuras); assegurar a confidencialidade e a privacidade, proteção da imagem e a não estigmatização, garantindo a não utilização das informações em prejuízo das pessoas e/ou das comunidades, inclusive em termos de autoestima, de prestígio e/ou econômico/financeiro; garantir que o material biológico e os dados obtidos na pesquisa serão utilizados exclusivamente para a finalidade prevista e autorizada pelo participante; acolhimento pelo médico responsável participante do estudo.

Benefícios:

Não haverá benefícios diretos aos participantes do estudo. Entretanto, os benefícios indiretos incluem: o esclarecimento sobre a influência da alergia respiratória na efetividade da resposta imune humoral e celular a SARS-CoV-2 após a vacinação para COVID-19 e; avaliação da efetividade das vacinas para COVID-19 entre a população de Uberlândia-MG. Os resultados poderão contribuir para o constante aprimoramento das vacinas.

Comentários e Considerações sobre a Pesquisa:

1. Para garantir o sigilo de informações e a não identificação do participante retirar o item Nome do Participante do documento "PerfilPosVacinal.docx"



Continuação do Parecer: 4.950.436

=> ANÁLISE CEP/UFU: Pendência atendida

2. (7.4). Caso o participante tenha que se deslocar para participar exclusivamente da pesquisa, deixar claro essa informação no TCLE e considerar o gasto de transporte e lanche aos participantes, caso fiquem mais de 90 minutos realizando as atividades inerentes a pesquisa.

RESPOSTA PESQUISADORES: Foi adicionado o trecho: "Caso o seu tempo de permanência no Laboratório de Alergia/UFU ultrapasse 90 minutos, você será ressarcido com lanche e transporte".

ANÁLISE CEP/UFU: Parcialmente atendida. Segundo a Norma Operacional 01/2013, item 3, subitem e) , a equipe executora deverá mencionar no item ORÇAMENTO da Pesquisa os gastos com o transporte destes participantes. Descrever no Projeto, Formulário da Plataforma Brasil, bem como o ressarcimento mencionado no TCLE.

RESPOSTA PESQUISADORES: Foi adicionado o trecho "Caso o tempo de permanência no Laboratório de Alergia/UFU ultrapasse 90 minutos, o voluntário será ressarcido com lanche e transporte." (pág.7, linha 225). Também foi adicionado na Plataforma Brasil.

=> ANÁLISE CEP/UFU: Pendência atendida

3. (7.5). Acrescentar no Termo a realização do teste cutâneo de Puntura e os riscos da sua realização (mesmo que seja mínimo). Esclarecer quantas vezes será realizada essa técnica.

ANÁLISE CEP/UFU: Pendência atendida A informação sobre os riscos inerentes à coleta de sangue e teste cutâneo foi adicionada no TCLE, conforme recomendado.

Considerações sobre os Termos de apresentação obrigatória:
Foram apresentados.

Conclusões ou Pendências e Lista de Inadequações:

Os pesquisadores atenderam as pendências do parecer nº 4.944.831 de 31 de agosto de 2021.

Considerações Finais a critério do CEP:

OBS.: O CEP/UFU LEMBRA QUE QUALQUER MUDANÇA NO PROTOCOLO DEVE SER INFORMADA



UNIVERSIDADE FEDERAL DE
UBERLÂNDIA/MG



Continuação do Parecer: 4.959.436

IMEDIATAMENTE AO CEP PARA FINS DE ANÁLISE E APROVAÇÃO DA MESMA.

O CEP/UFU lembra que:

- a- segundo as Resoluções CNS 466/12 e 510/16, o pesquisador deverá manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda e responsabilidade, por um período mínimo de 5 (cinco) anos após o término da pesquisa;
- b- poderá, por escolha aleatória, visitar o pesquisador para conferência do relatório e documentação pertinente ao projeto.
- c- a aprovação do protocolo de pesquisa pelo CEP/UFU dá-se em decorrência do atendimento as Resoluções CNS 466/12, 510/16 e suas complementares, não implicando na qualidade científica do mesmo.

Orientações ao pesquisador :

- O participante da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 466/12 e 510/16) e deve receber uma via original do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado.
- O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou (Res. CNS 466/12), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa que requeiram ação imediata.
- O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS 466/12). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.
- Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, destacando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprobatório do CEP, para serem juntadas ao protocolo inicial (Res.251/97, item III.2.e).



Continuação do Parecer: 4.959.436

De acordo com as atribuições definidas na Resolução CNS 466/12, Resolução 510/16 e suas complementares, o CEP manifesta-se pela aprovação do protocolo de pesquisa proposto. O protocolo não apresenta problemas de ética nas condutas de pesquisa com seres humanos, nos limites da redação e da metodologia apresentadas.

Data para entrega de Relatório Final ao CEP/UFU: AGOSTO/2024.

* Tolerância máxima de 01 mês para atraso na entrega do relatório final.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB INFORMações_BÁSICAS_DO_PROJETO_1791027.pdf	03/09/2021 16:17:07		Aceito
Projeto Detalhado / Brochura Investigador	ProjetoCEP.docx	03/09/2021 16:16:38	Rafael de Oliveira Resende	Aceito
Outros	PerfilPosVacinal.docx	03/09/2021 16:16:11	Rafael de Oliveira Resende	Aceito
Parecer Anterior	RespostasParecerCEP2.pdf	03/09/2021 16:15:16	Rafael de Oliveira Resende	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	03/09/2021 16:13:32	Rafael de Oliveira Resende	Aceito
Folha de Rosto	folhaDeRostoSubm2Emesto.pdf	18/08/2021 10:56:59	Rafael de Oliveira Resende	Aceito
Parecer Anterior	RespostasParecerCEP.pdf	17/08/2021 13:52:56	Rafael de Oliveira Resende	Aceito
Outros	RCAT.docx	17/08/2021 11:49:10	Rafael de Oliveira Resende	Aceito
Outros	IPAQ.docx	17/08/2021 11:48:50	Rafael de Oliveira Resende	Aceito
Declaração de Manuseio Material Biológico / Biorepositório /	TermoRespBiorrepositorioAssinado.pdf	17/08/2021 11:47:59	Rafael de Oliveira Resende	Aceito



Continuação do Parecer: 4.959.436

Biobanco	TermoRespBiorrepositorioAssinado.pdf	17/08/2021 11:47:59	Rafael de Oliveira Resende	Aceito
Outros	ACT.docx	17/08/2021 11:46:23	Rafael de Oliveira Resende	Aceito
Outros	LattesEquipe.doc	20/07/2021 18:37:57	Rafael de Oliveira Resende	Aceito
Declaração de Pesquisadores	TermocompromissoAssinado3.pdf	20/07/2021 16:27:01	Ernesto Akio Taketomi	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

UBERLÂNDIA, 08 de Setembro de 2021

Assinado por:
Karine Rezende de Oliveira
(Coordenador(a))