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Programa de Pós-Graduação *Stricto Sensu* em Ciências da Reabilitação
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A IDENTIFICAÇÃO DE DETERMINADAS CARACTERÍSTICAS CLÍNICAS QUE PODEM INTERFERIR NO QUADRO CLÍNICO E NO TRATAMENTO DE PACIENTES COM DORES MUSCULOESQUELÉTICAS

RIO DE JANEIRO
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Prefácio

Essa tese de doutorado apresenta tópicos relacionados à identificação de determinadas características clínicas que podem interferir no quadro clínico e no tratamento de pacientes com dores musculoesqueléticas. A presente tese está dividida em duas partes, considerando as normas vigentes do programa de Pós-Graduação em Ciências da Reabilitação do Centro Universitário Augusto Motta (UNISUAM). A primeira parte dessa tese é chamada de “Capítulo 1 – Projetos Desenvolvidos”. Diversas características clínicas interferem no quadro clínico de pacientes com dores musculoesqueléticas que podem ser identificadas como um particular fenótipo. O propósito dos artigos apresentados é enfatizar a necessidade de identificar os fatores presentes nos diferentes fenótipos de dor musculoesquelética. Por exemplo, o baixo nível de letramento em saúde (**subtópico 1.2.1**) e a presença de fatores emocionais em pacientes com fibromialgia (**subtópico 1.2.2**) estão associados à fenótipos particulares de dor. Além disso, cerca de 20% dos pacientes com dores musculoesqueléticas apresentam comprometimento da via descendente inibitória da dor e a sua identificação clínica permanece desafiadora. Exploramos modelos estatísticos para identificar o comprometimento da via descendente inibitória da dor no **subtópico 1.2.3.** Os dois projetos seguintes enfatizam a seleção de tratamentos específicos de acordo com a condição clínica do paciente. O **subtópico 1.3.2** aborda uma carta ao editor a fim de orientar os fisioterapeutas sobre o fornecimento adequado do tratamento da dor após um episódio de coronavírus 2019 (COVID-19). Por fim, apresentaremos uma revisão sistemática que é direcionada para a escolha de uma abordagem fisioterapêutica (mobilização neural) para pacientes com dor neuropática periférica, evidenciando a necessidade de fornecer um tratamento específico para um fenótipo com características clínicas particulares. De acordo com a Classificação Internacional de Doenças – CID 11, o que denominados, nesta tese como dor musculoesquelética crônica (dor lombar inespecífica) deve ser chamada de dor musculoesquelética crônica primária. Da mesma forma, a fibromialgia e a dor espalhada devem ser reconhecidas como síndromes de dor crônica primária. A segunda parte dessa tese é denominada “Capítulo 2 – Produção Intelectual” e apresenta 05 (cinco) artigos publicados e 01 (um) artigo em processo de submissão. No tópico “Disseminação da Produção” estão listados os artigos publicados, os artigos

aceitos e os artigos em submissão, incluindo os artigos em que a autora participou como colaboradora. Além disso, nesse tópico foram apresentados outros produtos resultantes do período do Doutorado, tais como: participação e organização de eventos científicos, publicações de resumos em anais de eventos científicos, prêmios recebidos, entre outros.

Resumo

Introdução: Estudar a dor musculoesquelética é importante porque trata-se de um problema de saúde comum e impactante que afeta indivíduos, sistemas de saúde e a sociedade em geral. Novos estudos permitem melhorar o diagnóstico e o tratamento dessa condição. Portanto, a presente tese objetivou identificar determinadas características clínicas que podem interferir no quadro clínico e no tratamento de pacientes com dores musculoesqueléticas.
Métodos: Essa tese foi composta por 06 (seis) artigos com diferentes delineamentos de estudo de acordo com cada objetivo. Três artigos transversais investigaram potenciais características clínicas que podem interferir no quadro clínico de pacientes com dores musculoesqueléticas. Um artigo avaliou a correlação entre o índice de dor espalhada e o software painMAP para avaliar as áreas de dor em pacientes com dor espalhada. Um editorial fornece orientação aos fisioterapeutas sobre o tratamento da dor após o coronavírus 2019 (COVID-19). Uma revisão sistemática visou identificar o efeito neurofisiológico da mobilização neural em pacientes com o fenótipo de dor neuropática.
Resultados: O **subtópico 2.2.1** mostra que pacientes com letramento em saúde inadequado tiveram níveis mais elevados de intensidade da dor e a cinesiofobia em comparação aos demais grupos. O **subtópico 2.2.2** revela que pacientes com fibromialgia possuem níveis mais elevados de intensidade de dor, presença de sintomas neuropáticos e presença de sintomas de sensibilização central, quando comparados a pacientes com dor espalhada. A mesma população foi investigada no **subtópico 2.2.3** que verificou uma correlação positiva fraca entre o índice de dor espalhada e o software painMAP para avaliar as áreas de dor em pacientes com dor espalhada. Os resultados do **subtópico 2.2.4** revelaram que o XGBoost possui potencial na previsão da eficácia da modulação condicionada da dor em pacientes com dor musculoesquelética. A carta apresentada no **subtópico 2.2.5** orienta os fisioterapeutas sobre o fornecimento do tratamento da dor após um episódio de coronavírus 2019 (COVID-19). A revisão sistemática apresentada no **tópico 3.1** mostra que há melhora na área de secção transversa de pacientes com dor neuropática periférica após a mobilização neural de acordo com evidências de qualidade muito baixa. Além disso, evidências de qualidade muito baixa a moderada sugere que a mobilização neural foi superior ao controle na melhoria da velocidade de condução motora e sensorial em pacientes com dor neuropática periférica.
Conclusão: A presente tese apresenta uma série de achados importantes relacionados à dor musculoesquelética, incluindo a influência do letramento em saúde, características de dor em pacientes com fibromialgia, correlação entre índice de dor espalhada e software painMAP, a eficácia do modelo treinado utilizando o algoritmo (XGBoost) na previsão da modulação condicionada da dor, orientações para tratamento fisioterapêutico pós-COVID-19 e que a mobilização neural foi capaz de melhorar a área de secção transversa (evidências de qualidade muito baixa) e as velocidades de condução motora e sensorial (evidências de qualidade muito baixa a moderada) em pacientes com dor neuropática periférica. Esses resultados destacam a complexidade da dor musculoesquelética e oferecem percepções valiosas para profissionais de saúde e pesquisadores, contribuindo para um melhor entendimento e manejo dessa condição clínica.

Palavras-chave: Dor musculoesquelética; Medição da dor; Manipulações musculoesqueléticas; Revisão sistemática.

Abstract

Introduction: Studying musculoskeletal pain is important because it addresses a common and impactful health issue affecting individuals, healthcare systems, and society. New studies can improve the diagnosis and treatment of this condition. Therefore, the present thesis aimed to identify specific clinical characteristics that may interfere with the clinical presentation and treatment of patients with musculoskeletal pain.

Methods: This thesis comprised 06 (six) articles with different study designs for each objective. Three (03) cross-sectional articles investigated potential clinical characteristics that can interferes with the clinical feature of patients with musculoskeletal pain. One article evaluated the correlation between the widespread pain index and the painMAP software to assess areas of pain in patients with widespread pain. One letter to the editor advices physiotherapists on pain treatment after the 2019 coronavirus (COVID-19). One systematic review aimed to identify the neurophysiological effects of neural mobilisation in patients with neuropathic pain phenotype.

Results: The **subtopic 2.2.1** shows that patients with inadequate health literacy had higher levels of pain intensity and kinesiophobia compared to other groups. The **subtopic 2.2.2** reveals that patients with fibromyalgia higher levels of pain intensity, presence of neuropathic symptoms, and presence of central sensitisation symptoms, compared to patients with widespread pain. The same population was investigated in **subtopic 2.2.3** which concludes a weak positive correlation between the widespread pain index and the painMAP software for assessing pain areas in patients with widespread pain. The results of **subtopic 2.2.4** revealed that the model trained using the algorithm (XGBoost) has the potential to predict the effectiveness of conditioned pain modulation in patients with musculoskeletal pain. The letter to the editor presented in **subtopic 2.2.5** advices physiotherapists in providing pain treatment after an episode of 2019 coronavirus (COVID-19). The systematic review in the **topic 3.1** shows an improvement in the cross-sectional area of patients with peripheral neuropathic pain after neural mobilisation, according to very low-quality evidence. Furthermore, very low to moderate-quality evidence suggests that neural mobilisation was superior to control

in improving motor and sensory conduction velocity in patients with peripheral neuropathic pain.

Conclusion: This thesis presents a series of important findings related to musculoskeletal pain, including the influence of health literacy, pain characteristics in patients with fibromyalgia, the correlation between widespread pain index and painMAP software, the effectiveness of XGBoost in predicting conditioned pain modulation, guidance for physiotherapeutic treatment after COVID-19, and the neural mobilisation was able to improve the cross-sectional area (evidence of very low quality) and motor and sensory conduction velocities (evidence of very low to moderate quality) in patients with peripheral neuropathic pain. These results highlight the complexity of musculoskeletal pain and offer valuable insights for healthcare professionals and researchers, contributing to a better understanding and management of this clinical condition.

Keywords: Musculoskeletal pain; Pain measurement; Musculoskeletal manipulations; Systematic review.

Lista de Quadros e Tabelas

Lista de Abreviaturas e Siglas

AINEs	Anti-Inflamatórios Não Esteroides
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CEP	Comitê de Ética em Pesquisa
CIs	Confidence Intervals
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
COBRAF	Congresso Brasileiro de Fisioterapia
COFIME	Congresso Internacional Online de Fisioterapia Musculoesquelética
COVID-19	Coronavírus 2019
CRediT	Contributor Roles Taxonomy
CSA	Cross-Sectional Area
CTS	Carpal Tunnel Syndrome
ENMG	Eletroneuromiografia
FAPERJ	Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro
FINEP	Financiadora de Estudos e Projetos
GRADE	Grading of Recommendations Assessment Development and Evaluation
IFRJ	Instituto Federal de Educação, Ciência e Tecnologia do Rio de Janeiro
MDs	Mean Differences
MeSH	Medical Subject Headings
NCS	Nerve Conduction Studies
ODS	Objetivos de Desenvolvimento Sustentável
OMS	Organização Mundial da Saúde
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
QES	Quasi-Experimental Study
RCT	Randomised Clinical Trials
RM	Ressonância Magnética
RoB	Risk of Bias tool
ROBINS-I	Risk of Bias in Non-randomised Studies
SUS	Sistema Único de Saúde
SWV	Shear Wave Velocity

TCLE	Termo de Consentimento livre e esclarecido
UNISUAM	Centro Universitário Augusto Motta
USI	Ultrassom por Imagem

Sumário

PARTE I – PROJETO DE PESQUISA

Capítulo 1 Projetos Desenvolvidos

1.1 Dor Musculoesquelética

As condições musculoesqueléticas são uma causa comum de dor e incapacidade em todo o mundo. Essas condições estão presentes em grande parte da população mundial e possuem um alto impacto socioeconômico. Atualmente, entre as condições musculoesqueléticas, a dor musculoesquelética é mais prevalente do que outros tipos de dor. De acordo com o *Global Burden of Disease* de 2016, a dor musculoesquelética atinge entre 20% a 33% da população mundial (1). Aproximadamente, 75% das consultas médicas tem a dor musculoesquelética como queixa principal (2,3). Considerando às características demográficas e estilos de vida, espera-se um aumento de até 50% na prevalência da dor musculoesquelética até o ano de 2050 (4). Portanto, a dor musculoesquelética têm sido considerada como um problema de saúde mundial uma vez que é uma condição com alta prevalência e onerosa economicamente (5–7).

O impacto socioeconômico das condições musculoesqueléticas é relevante tanto para o indivíduo em particular, como para a toda a sociedade. Os gastos com as a dor musculoesqueléticas superam os gastos com as doenças cardiovasculares, câncer e diabetes, quando combinados (8). Um estudo realizado nos Estados Unidos da América revelou que um em cada dois adultos americanos possui uma condição de dor musculoesquelética (9). Além disso, na Europa e nos Estados Unidos da América, aproximadamente metade da população sofre de dor musculoesquelética (10–12). Estima-se que 100 milhões de indivíduos sejam acometidos pela dor musculoesquelética nos Estados Unidos da América, resultando num custo anual de até 635 bilhões de dólares (13). Uma Pesquisa Nacional de Saúde realizada no Brasil revelou que 43% da população possui problemas de saúde musculoesquelética (14,15).

1.2 Fenótipos da Dor Musculoesquelética

Diversas condições de saúde podem afetar os músculos, ossos, articulações e estruturas relacionadas. A dor musculoesquelética se desenvolve a partir de lesões nos ossos, músculos, ligamentos, tendões ou nervos (16). Artrite reumatoide, osteoartrite, gota, dor lombar e dor cervical são exemplos de condições musculoesqueléticas (17). Portanto, compreender essa variedade de condições musculoesqueléticas, desde lesões específicas até doenças crônicas (artrite reumatoide e osteoartrite) é essencial para o manejo de pacientes com dor musculoesquelética.

A identificação dos fenótipos de dor musculoesquelética desempenha um papel crucial para a compreensão da complexidade das condições de dor. Os fenótipos de dor podem ser classificados de acordo com a localização (local ou difusa), com a duração da dor (aguda, crônica ou recorrente) ou de acordo com os mecanismos de dor (dor nociceptiva, dor neuropática ou dor nociplástica) (18). Assim, uma classificação baseada nos fenótipos é abrangente e proporciona uma base sólida para a identificação adequada do tipo de dor.

Os fenótipos de dor musculoesquelética abrangem um espectro diversificado de condições de dor com características clínicas distintas. Pacientes com artrite reumatoide podem apresentar sinovite, hipertrofia sinovial, lesão da cartilagem e do osso e presença de sintomas sistêmicos, resultando em dor e limitações funcionais (19). Pacientes com osteoartrite do joelho apresentam dor, rigidez, deformidade e perda de capacidade funcional (20,21). Pacientes com dor lombar apresentam uma diversidade de características, porém, àqueles com dor lombar relacionada aos membros inferiores têm pior prognóstico, maiores níveis de incapacidade, maior intensidade de dor e limitações funcionais em comparação com pacientes com dor lombar localizada (5–8). Além disso, pacientes com fibromialgia relatam pontos dolorosos espalhados, sensibilidade em pontos específicos e outros sintomas associados, como fadiga e distúrbios do sono (22,23). Apesar de todas as condições citadas anteriormente serem consideradas como condições musculoesqueléticas, as características clínicas são distintas. Portanto, o reconhecimento dessas características é crucial para que os profissionais de saúde ofereçam estratégias de tratamento adequadas.

1.2.1 Dor Musculoesquelética e Letramento em Saúde

O letramento em saúde refere-se as “habilidades cognitivas e sociais, que determinam a motivação e a capacidade dos indivíduos para obter acesso, compreender e utilizar a informação de forma a promover e manter uma boa saúde” (24). A tomada de decisão informada, o gerenciamento de medicamentos, a autogestão, a comunicação eficaz, a adesão aos planos de tratamento, a prevenção e educação, a redução das disparidades na saúde e a relação custo-benefício são exemplos de ações tomadas pelos pacientes que são possíveis a partir de um letramento em saúde adequado.

O letramento em saúde pode ser classificado como adequado, marginal ou inadequado. Baixos níveis de letramento em saúde são observados na Europa, variando entre 24% nos Países Baixos, 40% na Irlanda e 63% em Espanha (25). Nos Estados Unidos da América, aproximadamente 36% das pessoas foram classificadas como básicas ou abaixo dos níveis básicos de letramento em saúde (26). No Brasil, 32% dos adultos da população geral e 51% dos idosos apresentam baixo letramento em saúde (27).

Diversos aspectos podem contribuir para os níveis de letramento em saúde. Pessoas com baixos níveis socioeconômicos ou baixos níveis de escolaridade têm maior probabilidade de apresentar baixo letramento em saúde (25,28). Os baixos níveis de letramento em saúde estão associados a piores resultados de saúde (29,30) e à utilização inadequada dos serviços de saúde (31). Além disso, baixos níveis de letramento em saúde também estão associados a menor conhecimento e compreensão relacionados à saúde, aumento de hospitalizações e cuidados de emergência, maior mortalidade e estado geral de saúde (31,32). Assim, a identificação e classificação dos pacientes com dor musculoesquelética de acordo com os níveis de letramento em saúde permite o manejo adequado desses pacientes.

A dor musculoesquelética crônica, como dor nas costas e dor no pescoço, são condições prevalentes (33), nas quais baixos níveis de letramento em saúde podem impactar o quadro clínico. Por exemplo, pacientes com dor crónica e baixo letramento em saúde apresentaram menor conhecimento geral sobre medicamentos para a dor (34), tiveram valores mais altos de intensidade de dor (35–37) e a função física mais comprometida (37) do que pacientes com letramento em saúde adequado. Achados semelhantes foram observados em outras condições de dor musculoesquelética

(34,38). Pacientes com dor lombar relataram mais dificuldades em buscar, compreender e usar informações médicas em comparação com pacientes sem dor lombar crônica (38). Para avaliar o letramento em saúde de pacientes com dores musculoesqueléticas, os profissionais de saúde podem utilizar ferramentas padronizados, como o Teste Curto de Literacia Funcional em Saúde em Adultos (39,40) ou a Estimativa Rápida de Literacia em Medicina de Adultos (41). Além disso, os profissionais de saúde devem adotar estratégias de comunicação centradas no paciente, tais como a utilização de linguagem simples, recursos visuais e técnicas de ensino, para melhorar a compreensão e promover o letramento em saúde.

Embora estudos anteriores tenham avaliado as características da dor e a limitação funcional de acordo com os diferentes níveis de letramento em saúde dos pacientes, nenhuma evidência considerou os fatores psicológicos e sociais relacionados à dor. Assim, realizamos um estudo transversal em 243 pacientes com dor musculoesquelética crônica a fim de comparar a interferência relacionada à dor (intensidade da dor e limitação funcional) e fatores psicológicos e sociais relacionados à dor (fatores psicossociais) de acordo os níveis de letramento em saúde (inadequado, marginal e adequado). Os achados desse estudo estão apresentados no **subtópico 2.2.1.**

1.2.2 Características de Dor de Pacientes com Fibromialgia *versus* Dor Espalhada

A fibromialgia e a dor espalhada prevalecem nas condições de saúde musculoesquelética. A prevalência da fibromialgia foi de 4,7% na Europa (42), 6,4% nos Estados Unidos (43), 4,4% (44) no Brasil e 2%-3% na população em geral (45,46). A prevalência de dor crônica espalhada foi de 24% em mulheres brasileiras (44), e 10,6% (47) ou um em cada dez indivíduos são afetados por dor crônica espalhada na população em geral (47). Pacientes com fibromialgia apresentam dor musculoesquelética espalhada, fadiga, distúrbios do sono e alterações cognitivas (22,23).

A fibromialgia e a dor espalhada são condições que envolvem características similares como a presença de dor crônica. A fibromialgia é uma condição específica caracterizada por dor musculoesquelética espalhada, sensibilidade em pontos específicos e outros sintomas associados, como fadiga e distúrbios do sono (22,23).

A dor espalhada pode estar associada à fadiga, sofrimento psicológico e problemas de concentração assim como a fibromialgia (22,48). As duas condições são igualmente incapacitantes (44), mas a fibromialgia tem apresentação clínica desfavorável em comparação com a dor crônica espalhada (49,50). Pacientes com fibromialgia apresentam dor mais intensa e persistente do que pacientes com dor crônica espalhada (50). Além disso, os pacientes com fibromialgia apresentam mais comorbidades, uso de medicamentos relacionados à dor, pior estado de saúde, funcionalidade, sono, menor produtividade e custos mais elevados em comparação com pacientes sem dor crônica espalhada e com dor crônica espalhada, mas sem fibromialgia (51). Portanto, compreender as diferenças entre essas condições pode ajudar os profissionais de saúde a prestar melhores cuidados e apoio aos indivíduos que sofrem destas condições.

Vários instrumentos estão disponíveis para avaliação da fibromialgia e da dor espalhada. Os critérios preliminares para classificação da fibromialgia surgiram em 1990 (52). Na última atualização, uma combinação do Índice de Dor Espalhada (que foi projetado inicialmente para avaliar a distribuição da dor (48)), da Escala de Gravidade dos Sintomas (que avalia sintomas cognitivos e somáticos gerais (53)) e a combinação dos dois que resultam na Escala de Angústia Polissintomática (que mede a gravidade dos sintomas da fibromialgia) têm sido recomendados como critérios diagnósticos (48). Ao distinguir entre estas condições, os profissionais de saúde podem criar planos de tratamento personalizados que visam os desafios únicos que cada paciente enfrenta. Isso pode resultar em melhor alívio da dor e melhora geral na qualidade de vida do paciente.

Estudos comparativos das características da dor podem melhorar a nossa compreensão tanto da dor espalhada como da fibromialgia, o que pode proporcionar opções de tratamento mais eficazes, bem como resultar no desenvolvimento de ferramentas que podem ajudar na identificação das características de cada condição em particular e possíveis medidas preventivas. Nessa linha, essa tese apresenta o resultado de dois artigos. O **subtópico 2.2.2** descreve a comparação das características da dor e a limitação funcional de pacientes com fibromialgia e dor espalhada. O **subtópico 2.2.3** investiga a relação entre o índice de dor espalhada e o software painMAP para medir as áreas de dor na mesma população.

1.2.3 Modelos de Aprendizado de Máquina e Predição da Modulação Condicionada da Dor de Pacientes com Dor Musculoesquelética

O impacto dos estímulos dolorosos em seres humanos pode ser avaliado por meio de uma variedade de métodos. A abordagem mais popular para avaliar o aspecto central da dor é a modulação condicionada da dor (54). A modulação condicionada da dor é uma abordagem psicofísica que avalia como um estímulo teste é influenciado por um estímulo condicionante doloroso (55). Frequentemente, pacientes com dor musculoesquelética (56,57), dor crônica (58) e fibromialgia (59) apresentam comprometimento da modulação da dor condicionada. Estudos anteriores realizados pelo nosso grupo revelaram que entre 20% (60) e 25% (61) dos pacientes com dor musculoesquelética apresentavam comprometimento da modulação condicionada da dor. Assim, avaliar a modulação condicionada da dor em pacientes com dor musculoesquelética deve ser um objetivo tanto dos clínicos como dos pesquisadores em sua prática cotidiana.

Os modelos de aprendizado de máquina têm sido usados com frequência para identificar padrões em bases de dados e oferece o potencial para um manejo da dor musculoesquelética mais eficaz e baseado em dados, permitindo uma avaliação personalizada, o estabelecimento de metas e a melhoria dos resultados dos pacientes (62). Os modelos de aprendizado de máquina podem ajudar na compreensão de diversos aspectos relacionados à dor musculoesquelética. Estudos anteriores revelaram que esses modelos podem prever a recuperação em pacientes com lombalgia aguda (63) e identificar os pacientes com dor musculoesquelética que correm o risco de apresentar respostas inadequadas à modulação condicionada da dor (64). Portanto, ao prever as respostas da modulação condicionada da dor, os profissionais de saúde podem pensar em estratégias de tratamento com maior probabilidade de sucesso e a fim de melhorar os sintomas (aliviar a dor, reduzir a incapacidade e melhorar o seu bem-estar geral).

O **subtópico 2.2.4** apresenta um estudo exploratório transversal conduzido em 311 pacientes com dor musculoesquelética a fim de usar os modelos de aprendizado de máquina para estimar a eficácia da modulação condicionada da dor em pacientes com dor musculoesquelética.

1.3 Tratamento Fisioterapêutico

1.3.1 Tratamento da Dor Baseado em Mecanismo

Os mecanismos da dor referem-se a mecanismos neurofisiológicos que contribuem para o desenvolvimento ou manutenção da dor. A dor nociceptiva é o tipo mais comum de dor e normalmente é uma resposta direta a danos ou lesões nos tecidos. Esse tipo de dor é gerado quando receptores especializados no corpo, chamados nociceptores, detectam estímulos prejudiciais, como calor, pressão ou irritantes químicos (65). A dor nociceptiva geralmente é aguda e serve como mecanismo de proteção, alertando o corpo sobre uma lesão ou dano potencial. Os descritores mais comuns que caracterizam a dor nociceptiva incluem a presença de três sintomas (1. geralmente intermitente e aguda com movimento/provocação mecânica; pode ser uma dor latejante mais constante em repouso; 2. dor localizada na área da lesão/disfunção; e 3. natureza mecânica/anatômica clara e proporcional aos fatores agravantes e atenuantes), a ausência de três sintomas a saber: 1. dor descrita de várias maneiras como queimação, pontada, aguda ou semelhante a choque elétrico; 2. dor em associação com outras disestesias; e 3. dor noturna/sono perturbado e um sinal (posturas antálgicas/padrões de movimento) (66). O tratamento farmacológico da dor nociceptiva sugere o uso de anti-inflamatórios não esteroides (AINEs) ou opioides (67).

A dor neuropática é um tipo distinto de dor que se refere à dor causada por uma lesão ou doença do sistema somatossensorial (68). Esse tipo de dor surge quando os nervos ficam anormalmente sensibilizados e enviam sinais de dor ao cérebro na ausência de um estímulo nocivo. Os descritores mais comuns que caracterizam a dor neuropática incluem queimação, choques elétricos, dormência, coceira e agulhadas. Entre as suas principais causas estão: trauma, isquemia, infecção ou distúrbios metabólicos (69,70). O diagnóstico clínico da dor neuropática baseia-se na história clínica, exame clínico e nos testes quantitativos sensoriais a fim de identificar sinais e sintomas (hiperalgesia e alodinia) que coexistem com a alteração da função sensorial (hipoestesia ou déficits sensoriais) (71,72). A dor neuropática costuma ser crônica e pode ser difícil de controlar. As causas mais comuns de dor neuropática incluem: lesões nervosas (trauma ou compressão de nervos periféricos), doenças ou condições de saúde (neuropatia diabética, esclerose múltipla e herpes zoster) e distúrbios do

sistema nervoso central (danos ao cérebro ou à medula espinhal) (73). O tratamento da dor neuropática geralmente envolve medicamentos direcionados à dor relacionada aos nervos, como anticonvulsivantes, antidepressivos, medicamentos opioides e bloqueios nervosos (74).

A dor nociplástica é uma categoria de dor relativamente recente e ainda é pouco compreendida. A definição de dor nociplástica é a “dor que surge da nocicepção alterada, apesar de não haver evidência clara de dano tecidual real ou ameaçado, causando a ativação de nociceptores periféricos ou evidência de doença ou lesão do sistema somatossensorial causador da dor” (75). A dor nociplástica não tem uma causa clara, o que torna um pouco difícil diagnosticar e tratar essa condição. Acredita-se que a dor nociplástica resulta de alterações na forma como o sistema nervoso processa os sinais de dor, potencialmente devido a fatores como sensibilização, amplificação ou disfunção das vias da dor (76). As condições de saúde frequentemente associadas à dor nociplástica incluem fibromialgia, síndrome do intestino irritável e dor pélvica crônica (76). Diagnosticar e tratar a dor nociplástica pode ser complexo. O tratamento de pacientes com essa condição envolve uma abordagem multidisciplinar, incluindo tratamento farmacológico (antidepressivos, inibidores da recaptação de serotonina e norepinefrina, bloqueadores dos canais de cálcio e cetamina), fisioterapia, terapia cognitivo-comportamental e medicamentos que modulam a percepção da dor (67,77–79).

1.3.2 Tratamento Fisioterapêutico após COVID-19

A pandemia do coronavírus 2019 (COVID-19) é um problema de saúde em todo o mundo. A COVID-19 é uma condição infecciosa causada pelo vírus coronavírus-2 da síndrome respiratória aguda grave e foi reconhecida como uma pandemia global em março de 2020 (80). De acordo com a Organização Mundial da Saúde (OMS), mais de dois milhões de mortes foram causadas pelo COVID-19 até março de 2021 (81). No Brasil, o número de casos confirmados e mortes por COVID-19 foi superior a 12,9 e 328 milhões (81).

Os fisioterapeutas devem estar cientes de que os pacientes pós-COVID-19 podem relatar vários problemas de saúde (musculoesqueléticos e/ou neurológicos). Os sintomas musculoesqueléticos mais comuns incluem mialgia (19%), dor de cabeça (12%) e dor nas costas (10%) (82). No Brasil, os pacientes com COVID-19

apresentaram mialgia, fadiga e cefaleia como sintomas iniciais (83). Além disso, está bem estabelecido que a COVID-19 apresenta complicações neurológicas periféricas ou centrais (84). Comprometimento do olfato (35%), comprometimento do paladar (33%), tontura (10%), doença cerebrovascular aguda (3%) e ataxia (3%) são exemplos de manifestações neurológicas relatadas por pacientes com COVID-19 (82). Neuralgia, hiperalgesia e alodinia são outros sintomas neurológicos presentes em pacientes com COVID-19 (85). Portanto, discutir a abordagem do tratamento fisioterapêutico após a COVID-19 é essencial. O **subtópico 2.2.5** apresenta uma carta ao editor escrita no período da pandemia do coronavírus 2019 (COVID-19). O objetivo dessa carta é alertar e orientar os fisioterapeutas sobre o fornecimento adequado do tratamento da dor após um episódio de COVID-19.

1.3.3 Tratamento Fisioterapêutico para Dor Neuropática Periférica

A dor neuropática é uma das principais causas de sofrimento e incapacidade. Na população geral, a prevalência de dor neuropática crônica varia entre 7% e 10% (86). A dor neuropática está associada a muitas condições musculoesqueléticas, como dor lombar (87), distúrbios associados ao efeito chicote (88,89), epicondilalgia lateral (90), e síndrome do túnel do carpo (91).

Poucos tratamentos estão disponíveis para dor neuropática periférica. As diretrizes clínicas recomendam o manejo farmacológico como tratamento para pacientes com dor neuropática (92–95), incluindo antidepressivos tricíclicos, inibidores da recaptação de serotonina-norepinefrina e gabapentina como tratamentos de primeira linha (92,93,96). Além disso, abordagens não farmacológicas, como tratamentos conservadores como exercícios e terapia manual também têm sido recomendados para esses pacientes (97). Nos casos em que os pacientes não respondem adequadamente aos tratamentos anteriores, procedimentos invasivos podem ser considerados (98). Considerando os efeitos adversos causados pelas intervenções farmacológicas, as recomendações disponíveis ainda são inconsistentes (99). Assim, são necessárias abordagens eficazes e seguras para pacientes com dor neuropática periférica.

A mobilização neural é utilizada para atingir as estruturas neurais ou tecidos adjacentes e pode ser realizada manualmente (100,101). A mobilização neural promove benefícios clínicos para pacientes com doenças relacionadas aos nervos

(102–104). Por exemplo, a mobilização neural beneficia pacientes com dores nas costas e no pescoço (102). Da mesma forma, a mobilização neural apresentou efeitos moderados na flexibilidade de participantes saudáveis e grandes efeitos na intensidade da dor e incapacidade na dor lombar (103). Além disso, a mobilização neural teve resultados positivos moderados a grandes na intensidade da dor e incapacidade em pacientes com distúrbios musculoesqueléticos (105). Estudos anteriores também demonstraram que a mobilização neural reduz o edema intraneural (106) e melhora a dispersão do líquido intraneural (107,108). Houve um aumento simultâneo na magnitude do movimento neural adaptativo durante o teste de elevação da perna esticada e a resolução dos sintomas de dor radicular e lombar (109). Embora evidências de alta qualidade demonstrem o benefício clínico da técnica de mobilização neural, os efeitos da técnica na função e estrutura nervosa ainda não foram adequadamente explorados e resumidos.

Os nervos periféricos e suas propriedades mecânicas têm sido extensivamente estudados. Os nervos periféricos saudáveis apresentam forma tubular, alternando zonas hipoecogênicas e hipercogênicas correspondentes a fibras nervosas e perineural visíveis no Ultrassom por Imagem (USI) (110). Alterações na estrutura nervosa são comumente observadas em pacientes com neuropatias periféricas. Por exemplo, pacientes com síndrome do túnel do carpo apresentaram aumento na área de secção transversal do nervo mediano, hipoecogenicidade, distúrbio da estrutura fascicular, redução do deslizamento do nervo e aumento da vascularização (111). Da mesma forma, pacientes com neuropatia por compressão do nervo fibular demonstraram um aumento na área de secção transversal do nervo e um aumento na proporção de edema da fossa fibular para poplítea (111).

Vários instrumentos têm sido utilizados para avaliar a estrutura e função dos nervos periféricos. Testes de condução nervosa como a eletroneuromiografia (ENMG) e exames de imagem como a USI e a ressonância magnética (RM) são os mais utilizados. A área de secção transversa e a ecogenicidade dos nervos periféricos podem ser quantificadas pela USI (111,112). A ENMG pode ser usada na classificação de neuropatias (113), na avaliação da condução nervosa (114) e os achados da ENMG estão correlacionados com anormalidades estruturais no nervo (115). A USI geralmente mede a excursão dos nervos periféricos (116,117). Além disso, o método de RM tem sido utilizado em neuropatias periféricas para oferecer características mais quantitativas (118).

Por isso, **tópico 3.1** apresenta uma revisão sistemática da literatura sobre os efeitos da mobilização neural na função e na estrutura do nervo de pacientes com dor neuropática periférica.

1.4 Justificativas

1.4.1 Relevância para as Ciências da Reabilitação

Estudar a dor musculoesquelética é relevante porque aborda um problema de saúde comum e impactante que afeta indivíduos, sistemas de saúde e a sociedade em geral. Ao estudar a dor musculoesquelética, as ciências da reabilitação podem concentrar-se em: 1. compreender as causas e mecanismos subjacentes da dor musculoesquelética visto que é crucial para o desenvolvimento de programas de reabilitação eficazes; 2. identificar fatores de risco e sinais de alerta, sendo vital para medidas preventivas e intervenção precoce; 3. pensar em estratégias eficazes para o tratamento desses pacientes, uma vez que o conhecimento da dor musculoesquelética permite que os especialistas forneçam cuidados centrados no paciente. Além disso, a pesquisa em dor musculoesquelética geralmente leva ao desenvolvimento de novas tecnologias e ferramentas que podem auxiliar na avaliação, diagnóstico e tratamento.

1.4.2 Relevância para a Agenda de Prioridades do Ministério da Saúde[1]

O presente estudo enquadra-se na linha temática de diagnóstico e tratamento das doenças crônicas não-transmissíveis do Plano de Ação em Ciência, Tecnologia e Inovação para Saúde elaborado pelo Ministério da Ciência, Tecnologia e Inovação, o Ministério da Saúde e as agências de fomento Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) e Financiadora de Estudos e Projetos (FINEP). Segundo a Organização Pan-Americana da Saúde, as doenças crônicas não-transmissíveis representam as principais causas de mortalidade e de incapacidade prematura na maioria dos países de nosso continente, incluindo o Brasil.

[1] https://bvsms.saude.gov.br/bvs/publicacoes/agenda_prioridades_pesquisa_ms.pdf

Importa notar ainda que o tratamento e a assistência associados às doenças crônicas não-transmissíveis têm alto impacto para o Sistema Único de Saúde (SUS).

1.4.3 Relevância para o Desenvolvimento Sustentável[2]

O presente estudo está alinhado aos Objetivos de Desenvolvimento Sustentável (ODS) por meio da ODS 3 (assegurar uma vida saudável e promover o bem-estar para todos, em todas as idades) e das metas 3.8 (assegurar o acesso a serviços essenciais de saúde de qualidade em todos os níveis de atenção e 3.b (apoiar a pesquisa e o desenvolvimento de tecnologias e inovações em saúde para as doenças não-transmissíveis e proporcionar o acesso a essas inovações incorporadas ao SUS).

1.3.1 Disponibilidade e acesso aos dados

Os dados serão disponibilizados a partir da solicitação aos pesquisadores responsáveis pelo estudo e da aprovação do comitê de ética em pesquisa.

1.4 Orçamento e apoio financeiro

Este estudo é financiado pela Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Código Financeiro 001 e pela Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de janeiro (FAPERJ) [número E-26/201.398/2021].

Quadro 1: Apoio financeiro.

CNPJ	Nome	Tipo de Apoio financeiro	E-mail	Telefone
00889834/0001-08	CAPES	Bolsa	prosup@capes.gov.br	(061) 2022-6250

[2] https://odsbrasil.gov.br/objetivo/objetivo?n=3

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PARTE II – PRODUÇÃO INTELECTUAL

Capítulo 2 Contextualização da Produção

2.1 Disseminação da Produção

2.1.1 Publicação de artigos em revistas científicas

Durante o doutorado, a autora principal contribuiu com a disseminação de relevante conteúdo sobre a dor musculoesquelética, com a publicação de diversos artigos. Em 2021, o primeiro artigo abordou o letramento em saúde, a interferência da dor e os fatores psicológicos e sociais relacionados à dor em pacientes com dor musculoesquelética, publicado na *Health Promotion International*. No mesmo ano, um segundo artigo destacou a importância do manejo da dor em pacientes pós-covid-19, publicado na *Brazilian Journal of Physical Therapy*. No ano seguinte, em 2022, outro estudo revelou diferentes fenótipos de dor em pacientes com fibromialgia em comparação com aqueles com dor espalhada, publicado na *Brazilian Journal of Pain*. Finalmente, em 2023, um quarto artigo explorou a relação entre o Índice de Dor Espalhada e o software PainMAP na medição de locais de dor em pacientes com dor espalhada, também publicado na *Brazilian Journal of Pain*. Esses estudos contribuíram para o entendimento da complexidade da dor musculoesquelética e da necessidade de estratégias de manejo mais eficazes em diversas condições de saúde. O artigo final sobre o efeito da mobilização neural em pacientes com dores neuropáticas está em fase de submissão com provável publicação em 2024.

2.1.1.1 Artigos Publicados no Doutorado – Autora Principal

2021

1. **Bittencourt, Juliana Valentim**; de Souza, Patrick Anderson Chaves; Corrêa, Leticia Amaral; Volotão, Andresa Narcizo; Mathieson, Stephanie; Nogueira, Leandro Alberto Calazans. **Health literacy, pain-related interference and pain-related distress of patients with musculoskeletal pain.** O artigo referente ao **subtópico 2.2.1** desta tese foi publicado na *Health Promotion International*, volume 1, páginas 1-9, 2021.

2. **Bittencourt, Juliana Valentim**; Reis, Felipe José Jandre; Nogueira, Leandro Alberto Calazans. **Pain in COVID-19 patients: a call to action for physical therapists to provide pain management after an episode of COVID-19.** O artigo referente ao **subtópico 2.2.5** desta tese foi publicado na *Brazilian Journal of Physical Therapy*, volume 25, página 367, 2021.

2022

3. **Bittencourt, Juliana Valentim**; Amaral, Leticia Corrêa; Cliton, Márcia Bezerra; Reis, Felipe José Jandre; de Luca, Katie; Nogueira, Leandro Alberto Calazans. **Patients with fibromyalgia present different pain phenotypes compared to patients with generalized pain.** O artigo referente ao **subtópico 2.2.2** desta tese foi publicado na *Brazilian Journal of Pain*, volume 5, páginas 119-126, 2022.

2023

4. **Bittencourt, Juliana Valentim**; Rio, Jéssica Martins; Amaral, Leticia Corrêa; Reis, Felipe José Jandre; Ferreira, Arthur Sá; Nogueira, Leandro Alberto Calazans. **Relationship between the Widespread Pain Index and the PainMAP software for pain sites measurement in patients with widespread pain.** O artigo referente ao **subtópico 2.2.3** desta tese foi publicado na *Brazilian Journal of Pain*, volume 6, páginas 1-10, 2023.

2.1.1.2 Artigos Publicados no Doutorado – Contribuições

2020

5. Bezerra, Mariana Alonso Monteiro; **Bittencourt, Juliana Valentim**; Nogueira, Leandro Alberto Calazans. **Manejo não medicamentoso da dor musculoesquelética crônica - uma abordagem multimodal.** Boletim da Sociedade de Reumatologia do Rio de Janeiro, volume 03/2020, páginas 30-38, 2020.

2021

6. Leivas, Eduardo Gallas; **Bittencourt, Juliana Valentim;** Ferreira, Arthur Sá; Nogueira, Leandro Alberto Calazans. **Is it possible to discriminate workers with a higher prevalence of low back pain considering daily exposure time in a work-**

related lumbar posture? A diagnostic accuracy study. *Ergonomics*, volume 15, páginas 1-9, 2021.

2022

7. Telles, Gustavo Felicio; Ferreira, Arthur Sá; Junior, Pedro Manoel Pena; Lemos, Thiago; **Bittencourt, Juliana Valentim;** Nogueira, Leandro Alberto Calazans. **Concurrent validity of the inertial sensors for assessment of balance control during quiet standing in patients with chronic low back pain and asymptomatic individuals.** *Journal of Medical Engineering & Technology*, volume 4, páginas 1-9, 2022.

8. Freitas, João Paulo; Corrêa, Leticia Amaral; **Bittencourt, Juliana Valentim;** Armstrong, Karine Marcondes; Nogueira, Leandro Alberto Calazans. **Immediate effects of spinal manipulation on painful sensitivity and postural stability in patients with chronic nonspecific low back pain: study protocol for a controlled randomised clinical trial.** *Trials*, volume 23, páginas 1-9, 2022.

9. Corrêa, Leticia Amaral; **Bittencourt, Juliana Valentim;** Mainenti Pagnez, Maria Alice; Mathieson, Stephanie; Saragiotto, Bruno Tirotti; Telles, Gustavo Felicio; Meziat-Filho, Ney; Nogueira, Leandro Alberto Calazans. **Neural management plus advice to stay active on clinical measures and sciatic neurodynamic for patients with chronic sciatica: Study protocol for a controlled randomised clinical trial.** *Plos One*, volume 17, páginas e0263152-15, 2022.

2023

10. Reis, Felipe José Jandre; **Bittencourt, Juliana Valentim;** Calestini, Lucas; Ferreira, Arthur Sá; Meziat-Filho, Ney; Nogueira, Leandro Alberto Calazans. **Exploratory analysis of 5 supervised machine learning models for predicting the efficacy of the endogenous pain inhibitory pathway in patients with musculoskeletal pain**. O artigo referente ao **subtópico 2.2.4** desta tese foi publicado na *Musculoskeletal Science and Practice*, volume 66, páginas 102788, 2023.

11. Goldoni, Enrico Seixas; **Bittencourt, Juliana Valentim;** Espirito Santo, Lanucia Ranhol do; Souza, Eduardo Branco de; Faria, José Leonardo Rocha de; Andrade, Dângelo Alexandre; Nogueira, Leandro Alberto Calazans. **Neuropathic-like symptoms and central sensitization related signs and symptoms negatively affect the functional performance of patients with knee osteoarthritis - a cross-sectional study.** *Osteoarthritis and Cartilage Open*, volume 5, páginas 100358-100368, 2023.

12. Corrêa, Leticia Amaral; **Bittencourt, Juliana Valentim;** Mathieson, Stephanie; Nogueira, Leandro Alberto Calazans. **Pain-related interference and pain-related psychosocial factors of three different subgroups of patients with chronic low back pain.** *Musculoskeletal Science and Practice*, volume 63, página 102718, 2023.

13. Dias, Paula Renata Conceição de Oliveira; **Bittencourt, Juliana Valentim;** Rio, Jéssica Pinto Martins do; Reis, Felipe José Jandre; Oliveira, Laura Alice Santos de; Nogueira, Leandro Alberto Calazans. **Pain interference, neuropathic-like symptoms, pain intensity, and symptoms of central sensitization negatively impact individual's disability after Chikungunya fever: cross-sectional study.** *Brazilian Journal of Pain*, volume 6, páginas 139-44, 2023.

2.1.1.3 Artigos do Mestrado Publicados nos Anos do Doutorado

14. Bezerra, Márcia Cliton; **Bittencourt, Juliana Valentim;** Reis, Felipe José Jandre; Almeida, Renato Santos; Meziat-Filho, Ney; Nogueira, Leandro Alberto Calazans. **Central Sensitization Inventory is a useless instrument for detection of the impairment of the conditioned pain modulation in patients with chronic musculoskeletal pain.** *Joint Bone Spine*, volume 88(3), página 105127, 2021, doi 10.1016/j.jbspin.2020.105127.

15. **Bittencourt, Juliana Valentim;** Pina, Mônica Rotondo; Reis, Felipe José Jandre; Arthur Sá; Nogueira, Leandro Alberto Calazans. **Use of the painDETECT to discriminate musculoskeletal pain phenotypes.** *Archives of Physiotherapy*, volume 12(7), páginas 1-8, 2022, doi 10.1186/s40945-022-00129-2.

2.1.1.4 Artigos Aceitos

Palma, Alanna Martins Soares de; Rio, Jéssica Pinto Martins do; **Bittencourt, Juliana Valentim;** Nogueira, Leandro Alberto Calazans. **Métodos para avaliação da modulação condicionada da dor em pacientes com distúrbios musculoesqueléticos: uma revisão de escopo da literatura.** Aceito na revista Arquivos Brasileiros de Educação Física em setembro de 2023.

2.1.1.5 Artigos Submetidos

Freitas, João Paulo; Corrêa, Leticia Amaral; **Bittencourt, Juliana Valentim;** Armstrong, Karine Marcondes; Meziat-Filho, Ney; Nogueira, Leandro Alberto Calazans. **One spinal manipulation session reduces lumbar pain sensitivity but does not affect postural stability in individuals with chronic low back pain: a randomised, placebo-controlled trial.** Submetido para a Chiropractic & Manual Therapies em 04/10/2023.

2.1.2 Prêmios e Outras Formas de Disseminação da Produção

Ao longo dos anos, a autora principal recebeu reconhecimento notável por suas contribuições na área da dor musculoesquelética. Em 2021, seu artigo sobre a precisão diagnóstica de indicadores clínicos na identificação da sensibilização central em pacientes com dor musculoesquelética foi o mais votado para tradução em português no TraduTERA. Em 2022, outro artigo, focado no uso do questionário painDETECT na discriminação de fenótipos de dor musculoesquelética, também foi traduzido pelo TraduTERA. Em 2023, um estudo de acurácia diagnóstica sobre a identificação da modulação condicionada da dor em pacientes com dor musculoesquelética foi escolhido como o artigo mais votado para tradução em português no TraduTERA.

2021 – Artigo mais votado para a tradução em português (mês de fevereiro) no TraduTERA. Artigo escolhido: “Diagnostic accuracy of the clinical indicators to identify central sensitization pain in patients with musculoskeletal pain”.

2021 – Resumo selecionado entre os 5 melhores trabalhos submetidos para o I Congresso Internacional Online de Fisioterapia Musculoesquelética (COFIME).

2022 – Artigo mais votado para a tradução em português (mês de abril) no TraduTERA. Artigo escolhido: “Use of the painDETECT to discriminate musculoskeletal pain phenotypes”.

2022 – Primeira Colocada no Processo Seletivo Simplificado para Contratação de Professor Substituto, Instituto Federal de Educação, Ciência e Tecnologia do Rio de Janeiro (IFRJ).

2023 – Artigo mais votado para a tradução em português (mês de outubro) no TraduTERA. Artigo escolhido: “Does the painDETECT questionnaire identify impaired conditioned pain modulation in people with musculoskeletal pain? – a diagnostic accuracy study”.

2.1.3 Participação em Eventos Acadêmicos

2019

1. XVII semana de pesquisa, extensão, pós-graduação e inovação da UNISUAM. Validade dos indicadores clínicos na identificação da sensibilização central em pacientes com dor musculoesquelética? Um estudo de acurácia diagnóstica. 2019.
2. XVI semana de pesquisa, extensão, pós graduação e inovação. Validação do inventário de sensibilização central como método padrão ouro para a identificação da sensibilização central em pacientes com dores musculoesqueléticas. 2019.
3. XVI semana de pesquisa, extensão, pós graduação e inovação. Adaptação transcultural do questionário paindetect para a língua portuguesa do Brasil. 2019.

2020

4. XVII semana de pesquisa, extensão, pós graduação e inovação. Pacientes com fibromialgia apresentam fenótipos de dor diferentes em comparação com pacientes com dor generalizada. 2020.
5. XVII semana de pesquisa, extensão, pós graduação e inovação. Adição de técnicas de gerenciamento neural a orientação a manter-se ativo nas medidas clínicas e na área do nervo ciático em pacientes com ciatalgia crônica: protocolo para um ensaio clínico randomizado controlado. 2020.
6. Annual scientific (virtual) meeting 2020 Sydney musculoskeletal, bone & joint health alliance. 2020.

7. VII semana de pesquisa, extensão, pós graduação e inovação. Pacientes com fibromialgia apresentam fenótipos de dor diferentes em comparação com pacientes com dor generalizada. 2020.
8. Webinar: ultrassonografia cinesiológica para fisioterapeutas. 2020.
9. XIV jornada interna de iniciação científica e tecnológica. Adaptação transcultural do questionário paindetect para a língua portuguesa do brasil. 2020.

2021

10. 1º congresso internacional online de fisioterapia musculoesquelética. 2021.
11. 1º congresso internacional online de fisioterapia musculoesquelética. Comparação das características da dor e da funcionalidade entre os pacientes com fibromialgia e os pacientes com dor generalizada. 2021.
12. V congresso brasileiro de fisioterapia na saúde da mulher. 2021.
13. VII jornada de iniciação científica do IFRJ. Métodos para avaliação da modulação condicionada da dor em pacientes com distúrbios musculoesqueléticos: uma revisão de escopo da literatura. 2021.
14. XVIII semana de pesquisa, extensão, pós graduação e inovação. Tratamento fisioterápico dos pacientes com dores ciáticas. 2021.
15. XXIII COBRAF - congresso brasileiro de fisioterapia. Validity of the clinical indicators to identify central sensitization pain in patients with musculoskeletal pain a diagnostic accuracy study. 2021.
16. XXIII COBRAF - congresso brasileiro de fisioterapia. 2021.

2022

17. X encontro da saúde do IFRJ - campus Realengo. Efeitos da mobilização neurodinâmica sobre a área seccional transversa, ecogencidade e distância do nervo ciático à pele em um participante saudável - relato de caso. 2022.
18. X encontro da saúde do IFRJ - campus Realengo. Medidas de ultrassom da área seccional transversa, ecogenicidade e distância do nervo à pele do nervo ciático em diferentes posições da perna - estudo de confiabilidade. 2022.
19. XVI jornada interna de iniciação científica e tecnológica (JIT 2022). Efeitos da mobilização neurodinâmica sobre a área seccional transversa, ecogencidade e distância do nervo ciático à pele em um participante saudável - relato de caso. 2022.

20. XVI jornada interna de iniciação científica e tecnológica (JIT 2022). Medidas de ultrassom da área seccional transversa, ecogenicidade e distância do nervo à pele do nervo ciático em diferentes posições da perna - estudo de confiabilidade. 2022.
21. XXIV congresso brasileiro de fisioterapia (COBRAF). 2022.

2023

22. I fórum discente da associação brasileira de pós-graduação - fisioterapia (ABRAPG-FT). Sintomas do tipo neuropático e sinais e sintomas relacionados à sensibilização central afetam negativamente o desempenho funcional de pacientes com osteoartrite de joelho? Um estudo transversal. 2023.
23. I fórum discente da associação brasileira de pós-graduação - fisioterapia (ABRAPG-FT). O questionário paindetect identificou corretamente a modulação condicionada da dor preservada na maioria dos pacientes com dor musculoesquelética. 2023.
24. I mostra de gestão da saúde pública carioca. 2023.
25. Seminário interno de meio termo do programa de pós-graduação em ciências da reabilitação do Centro Universitário Augusto Motta (PPGCR-UNISUAM). 2023.
26. XI encontro da saúde do IFRJ - campus Realengo. Mostra – VIII mostra CTACS. 2023.

2.1.4 Anais Publicados em Eventos Acadêmicos

Em 2021, Juliana Valentim Bittencourt e seus colaboradores deram contribuições significativas ao campo da fisioterapia e da pesquisa em dor musculoesquelética. O primeiro estudo comparou as características da dor e a funcionalidade entre pacientes que sofrem de fibromialgia e àqueles com dor espalhada. Esta pesquisa foi selecionada entre os cinco melhores resumos e foi publicada nos anais do I Congresso Internacional Online de Fisioterapia Musculoesquelética (COFIME). No mesmo ano, os resultados do estudo de acurácia diagnóstica avaliando a validade de indicadores clínicos para identificar a sensibilização central em pacientes com dor musculoesquelética foram apresentados no XXIII Congresso Brasileiro de Fisioterapia (COBRAF). Essas iniciativas

contribuíram significativamente para a compreensão da dor e suas implicações no cuidado ao paciente na área da fisioterapia e da saúde musculoesquelética.

2.1.4.1 Resumos Publicados em Anais de Eventos

AUTORA PRINCIPAL

2021

1. **Bittencourt, Juliana Valentim;** Corrêa, Leticia Amaral; Bezerra, Márcia Cliton; Reis, Felipe José Jandre; Luca, Katie; Nogueira, Leandro Alberto Calazans. **Comparação das características da dor e da funcionalidade entre os pacientes com fibromialgia e os pacientes com dor generalizada.** Publicado nos anais do I Congresso Internacional Online de Fisioterapia Músculoesquelética (COFIME), volume 4, página 46, 2021, doi 10.20873/abef.2595-0096.v4n1pg0140100.

2. **Bittencourt, Juliana Valentim;** Corrêa, Leticia Amaral; Nogueira, Leandro Alberto Calazans. **Validity of the clinical indicators to identify central sensitization pain in patients with musculoskeletal pain a diagnostic accuracy study.** Publicado nos anais do XXIII Congresso Brasileiro de Fisioterapia (COBRAF), 2021. Disponível em: <https://proceedings.science/cobraf/cobraf-2021/trabalhos/validity-of-the-clinical-indicators-to-identify-central-sensitization-pain-in-pa?lang=pt-br>. Acesso em: 25 set. 2023.

CONTRIBUIÇÕES

2021

3. Corrêa, Leticia Amaral; **Bittencourt, Juliana Valentim;** Nogueira, Leandro Alberto Calazans. **Pain-related interference and pain-related distress of three different phenotypes of patients with chronic low back pain.** Publicado nos anais do I Congresso Internacional Online de Fisioterapia Músculoesquelética (COFIME), volume 4, página 50, 2021, doi 10.20873/abef.2595-0096.v4n1pg0140100.

4. Corrêa, Leticia Amaral; **Bittencourt, Juliana Valentim;** Ferreira, Arthur Sá, Almeida, Renato Santos; Nogueira, Leandro Alberto Calazans. **Reliability and concurrent validity of the painmap for automated quantification of pain drawings in body charts in patients with low back pain.** Publicado nos anais do XXIII

Congresso Brasileiro de Fisioterapia (COBRAF), 2021. Disponível em: <https://proceedings.science/cobraf/cobraf-2021/trabalhos/reliability-and-concurrent-validity-of-the-painmap-for-automated-quantification?lang=pt-br>. Acesso em: 25 set. 2023.

5. Rio, Jéssica Pinto Martins do; **Bittencourt, Juliana Valentim;** Corrêa, Leticia Amaral; Nogueira, Leandro Alberto Calazans. **Adaptação transcultural do questionário paindetect para a língua portuguesa do Brasil.** Publicado nos anais do XXIII Congresso Brasileiro de Fisioterapia (COBRAF), 2021. Disponível em: <https://proceedings.science/cobraf/cobraf-2021/trabalhos/adaptacao-transcultural-do-questionario-paindetect-para-a-lingua-portuguesa-do-b?lang=pt-br>. Acesso em: 25 set. 2023.

6. Bezerra, Márcia Cliton; **Bittencourt, Juliana Valentim;** Nogueira, Leandro Alberto Calazans. **Validação do inventário de sensibilização central como método padrão ouro para a identificação da sensibilização central em pacientes com dores musculoesqueléticas.** Publicado nos anais do XXIII Congresso Brasileiro de Fisioterapia (COBRAF), 2021. Disponível em: <https://proceedings.science/cobraf/cobraf-2021/trabalhos/validacao-do-inventario-de-sensibilizacao-central-como-metodo-padrao-ouro-para-a?lang=pt-br>. Acesso em: 25 set. 2023.

2022

7. Moreira, Rayssa de Vilhena; Espirito Santo, Lanucia Ranhol do; **Bittencourt, Juliana Valentim;** Pagnez, Maria Alice Mainenti; Rio, Jéssica Pinto Martins; Nogueira, Leandro Alberto Calazans. **Medidas de ultrassom da área seccional transversa, ecogenicidade e distância do nervo à pele do nervo ciático em diferentes posições da perna - estudo de confiabilidade.** Publicado nos anais do X Encontro da Saúde do IFRJ – campus Realengo, 2022. Disponível em: www.even3.com.br/Anais/XEncontrodasaude/563208-MEDIDAS-DE-ULTRASSOM-DA-AREA-SECCIONAL-TRANSVERSA-ECOGENICIDADE-E-DISTANCIA-DO-NERVO-A-PELE-DO-NERVO-CIATICO-EM-

8. Moreira, Rayssa de Vilhena; Espirito Santo, Lanucia Ranhol do; **Bittencourt, Juliana Valentim;** Pagnez, Maria Alice Mainenti; Rio, Jéssica Pinto Martins; Nogueira, Leandro Alberto Calazans. **Efeitos da mobilização neurodinâmica sobre a área seccional transversa, ecogencidade e distância do nervo ciático à pele em um participante saudável - relato de caso.** Publicado nos anais do X Encontro da Saúde do IFRJ – campus Realengo, 2022. Disponível em: www.even3.com.br/Anais/XEcontrodasaude/563214-EFEITOS-DA-MOBILIZACAO-NEURODINAMICA-SOBRE-A-AREA-SECCIONAL-TRANSVERSA-ECOGENCIDADE-E-DISTANCIA-DO-NERVO-CIATICO.

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Article

OXFORD

Health literacy, pain-related interference and pain-related distress of patients with musculoskeletal pain

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Summary

The present study aimed to compare pain-related interference and pain-related distress in patients with musculoskeletal pain and differing levels of health literacy. A cross-sectional study was conducted among 243 patients with chronic musculoskeletal pain. Short Test of Functional Health Literacy in Adults classified the level of health literacy. Outcome measures included pain-related interference (pain intensity and functional limitation) and pain-related distress (psychosocial factors). Analysis of variance methods were used. One hundred twenty-three (50.62%) participants were classified as adequate, 24 (9.88%) as marginal and 96 (39.50%) as inadequate health literacy. Patients with inadequate health literacy had higher values of pain severity compared to the other groups, when controlled for age. The group adequate health literacy showed less kinesiophobia compared to their counterparts. Functional limitations and other psychosocial factors were similar among groups. Pain severity and kinesiophobia had disadvantageous findings in participants with inadequate health literacy. Still, the results of pain severity must be approached cautiously because the differences were observed when controlled for age solely.

Key words: musculoskeletal pain, chronic pain, pain education, health literacy

BACKGROUND

Health literacy is 'cognitive and social skills, which determine the motivation and ability of individuals to gain access to, understand and use information in ways that promote and maintain good health', according to World Health Organization (World Health Organization, 2009). Low levels of health literacy are observed in Europe, varying from 24% in the Netherlands, 40% in Ireland to 63% in Spain (HLS-EU Consortium, 2012). Approximately 36% of the people in the United States were classified as basic or below basic levels of health literacy (Kutner *et al.*, 2006). In Brazil, 32% of the

adults in the general population and 51% of older people present low health literacy (Carthery-Goulart *et al.*, 2009). The identification of patients presenting low levels of health literacy allows health professionals to offer strategies treatment and appropriate management to these patients.

Health literacy involves personal characteristics and social resources that are available to the individual. People with low socioeconomic status or low levels of education are more likely to present low health literacy (HLS-EU Consortium, 2012; Sørensen *et al.*, 2015). Low levels of health literacy are involved with poor health outcomes (Bostock and Steptoe, 2012; Campbell *et al.*, 2019) and inadequate use of health care services (Berkman *et al.*, 2011). Low levels of health literacy are also associated with poorer health-related knowledge and comprehension, increased hospitalizations and emergency care, higher mortality and general health status (DeWalt *et al.*, 2004; Berkman *et al.*, 2011). Moreover, prior studies showed the relationship between low health literacy and higher psychological distress. For instance, rheumatoid arthritis patients with high levels of health literacy were less anxious and depressed (Walker *et al.*, 2007). Besides, lower health literacy scores were observed in patients with chronic pain, anxiety or depression and arthritis (Jenkins *et al.*, 2017). Thus, research is needed to identify the impact of low health literacy on health outcomes of patients with different health conditions.

Chronic musculoskeletal pain, such as back and neck pain are prevalent conditions (James *et al.*, 2018), in which low levels of health literacy may impact the clinical presentation. For instance, patients with chronic pain and low health literacy presented poorer overall knowledge of pain medications (Devraj *et al.*, 2013), had higher rates of pain intensity (Van Hecke *et al.*, 2016; Köppen *et al.*, 2018; Lacey *et al.*, 2018) and lower physical function (Lacey *et al.*, 2018) than patients with adequate literacy. Similar findings have been observed in other musculoskeletal pain conditions (Briggs *et al.*, 2010; Devraj *et al.*, 2013). Low back pain patients reported more difficulties in seeking, understanding and using medical information compared to patients without chronic low back pain (Briggs *et al.*, 2010). However, a systematic review that includes studies from developed countries with a small sample size performed in patients with rheumatic diseases showed there is no consistent association between low health literacy and poorer functional outcomes (Loke *et al.*, 2012). Although the previous studies had assessed pain characteristics and functional limitation in patients' different levels of health literacy, no evidence has considered pain-related distress. Therefore, the current study aimed to compare pain-related interference (pain severity and functional limitation) and pain-related distress (symptoms of anxiety, symptoms of depression, perceived stress, social isolation, catastrophizing, kinesiophobia and maladaptive beliefs) in patients with musculoskeletal pain and differing levels of health literacy.

METHODS

Study design and ethical considerations

A cross-sectional study design reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) requirements (Von Elm *et al.*, 2007). This study was approved by the Research Ethics Committee of Federal Institute of Rio de Janeiro (number: 83321917.7.0000.5268), in accordance with the Helsinki Declaration for research in humans. All patients who met the eligibility criteria signed the informed consent form before the study procedures.

Eligibility criteria

Patients with musculoskeletal pain (aged 18 years and over) were selected by convenience when they sought treatment from two public physiotherapy outpatient departments (Gaffrée and Guinle University Hospital and Federal Institute of Rio de Janeiro) in Rio de Janeiro, Brazil, and one private physiotherapy outpatient in Minas Gerais, Brazil, between March and September 2019. The classification of musculoskeletal pain was performed by one physiotherapist (LACN) with 19 years of work experience in an outpatient department in treating patients with musculoskeletal disorders. The study included patients with chronic musculoskeletal pain (pain duration greater than three months). Musculoskeletal pain was defined as pain perceived in a region of the body with muscular, ligament, bone, or joint origin (Murray *et al.*, 2013). Patients who had a serious pathology (e.g. suspected fracture, tumours or cancer), rheumatologic diagnosis in the acute inflammatory phase (e.g. inflammatory arthritis or spondyloarthropathy), pregnant women, vulnerable patients (e.g. experienced recent trauma, cognitive impairment, or dementia), patients who present insufficient understanding of the Portuguese language or interpretation assistance available to complete the study treatment were excluded from the study.

Data collection

Patients were referred for an initial evaluation for data collection on sociodemographic [age, sex, weight, height,

body mass index (BMI) and education level] and outcome measures (pain-related interference—pain severity and functional limitation; pain-related distress—anxiety, social isolation, perceived stress, catastrophization, depression and kinesiophobia). All the data were collected using printed questionnaires. Patients completed the questionnaires in the presence of a study researcher in case clarification was needed. Patients took approximately 50 min to sign the informed consent form, to fill out sociodemographic and clinical characteristics and complete questionnaires.

Outcome measures

Health literacy classification

The Short Test of Functional Health Literacy in Adults (S-TOFHLA) is an instrument developed to assess the adult literacy in health-related subject and has a duration of around 7 min (Parker *et al.*, 1995; Baker *et al.*, 1999). Currently, S-TOFHLA is one of the most used instruments globally to assess the ability to read and understand items that have a specific meaning in the health area (Gordon *et al.*, 2002; Jordan *et al.*, 2011). S-TOFHLA has 40 items, including 4-item (28 points) of the test of numeracy skills and 36-item (72 points) of the reading and comprehension. The test of numeracy skills includes four questions that present information regarding medication instructions, test results and appointment date. Each correct answer corresponds to 7 points, and the maximum score for the first section is 28 points. The reading and comprehension section include 26 questions that refer to the preparation for a radiological examination and health administrative management. Each correct answer corresponds to 2 points, and the maximum score for the second section is 72 points. S-TOFHLA has a final score of 100 points. Scores between 67 and 100 points are considered an adequate health literacy, scores between 54 and 66 points are classified as marginal health literacy, and scores between 0 and 53 points are considered an inadequate health literacy (Parker *et al.*, 1995; Baker *et al.*, 1999). S-TOFHLA is considered equivalent to the original TOFHLA ($r = 0.91$) (Baker *et al.*, 1999), the reliability coefficients ranged from a low to a high (Spearman's correlation coefficient = 0.56 to 0.81) (Baker *et al.*, 1999; McNaughton *et al.*, 2011; Chang *et al.*, 2012), and presented a strong internal consistency (Cronbach's α coefficients = 0.90 to 0.97) (Baker *et al.*, 1999; Jović-Vraneš *et al.*, 2014). Permission to use the S-TOFHLA was obtained from the original developers of the questionnaire (Baker *et al.*, 1999) and authors responsible for translation and cross-cultural adaptation to the Brazilian context (Carthery-Goulart *et al.*, 2009).

Pain-related interference

Pain characteristics. Pain severity of the participants presenting musculoskeletal condition was measured during the evaluation using the Numeric Pain Rating Scale (NPRS) scored from 0 (no pain) to 10 (the worst possible pain) (Jensen and McFarland, 1993; Chapman *et al.*, 2011; Hawker *et al.*, 2011). NPRS is one of the most common outcome measures in chronic musculoskeletal pain (Chapman *et al.*, 2011) and has good levels of reproducibility (Hawker *et al.*, 2011). NPRS present high test–retest reliability ($r = 0.95$) in patients with rheumatoid arthritis (Downie *et al.*, 1978). Also, NPRS was highly correlated to the Visual Analog Scale in patients with many chronic pain conditions (Downie *et al.*, 1978; Ferraz *et al.*, 1990). Brazilian version of NPRS exhibited excellent reproducibility [ICC = 0.94; (95% CI: 0.90–0.96)] (Costa *et al.*, 2008).

Functional limitation. Functional limitation was evaluated using the Patient-Specific Functional Scale (PSFS). Participants identified up to five important activities they were unable to perform as a result of their pain problem. The level of difficulty of each activity was scored on an 11-point scale. PSFS has been reported to be valid, reliable and responsive clinical outcome measure in musculoskeletal conditions (Stratford *et al.*, 1995; Kowalchuk Horn *et al.*, 2012). Brazilian version of PSFS presents substantial reproducibility [ICC = 0.85; (95% CI: 0.77–0.90)] (Costa *et al.*, 2008). PSFS has excellent reliability, moderate construct validity correlation and moderate to strong longitudinal validity correlation compared to the other instruments (e.g. NPRS) in patients with upper extremity musculoskeletal disorders (Nazari *et al.*, 2020).

Pain-related distress

Pain-related distress is the multifactorial unpleasant emotional experience of a psychological, social, or spiritual nature (Treede *et al.*, 2019). Pain-related distress was measured using the Brief Screening Questions (BSQ) (Kent *et al.*, 2014). The screening encompasses psychosocial factors, including psychological factors (symptoms of anxiety, symptoms of depression and perceived stress), social isolation and cognitive factors (catastrophizing, kinesiophobia and maladaptive beliefs). Questions included the identification and quantification of symptoms of anxiety ('Do you feel anxious?'); symptoms of depression ('During the past month have you often been

bothered by feeling down, depressed or hopeless?' and 'During the past month have you often been bothered by little interest or pleasure in doing things?'); social isolation ('Do you feel socially isolated?'); catastrophizing ('When I feel pain, it's terrible and I feel it's never going to get any better' and 'When I feel pain, I feel I can't stand it anymore'); and kinesiophobia ('Physical activity might harm my back' and 'I should not do physical activities which (might) make my pain worse') were added as cognitive factors. The perceived stress assessment ('Do you feel stressed?') was performed by one item from the Brief Psychological Screening Questions (BPSQ) (Vaegter *et al.*, 2017). In both instruments, each question is rated between 0 (represents 'never do that' or 'not at all') and 10 (represents 'always do that' or 'quite'). The BSQ and BPSQ are used to evaluate the impact of psychosocial factors on the participants' health. BSQ presented high values of sensitivity (ranged from 70% to 82%) and specificity (ranged from 75% to 95%) in anxiety, depression and social isolation scores compared with standard reference questionnaires for each psychosocial factor. Sensitivity and specificity in catastrophization and fear of movement ranged from 78% to 88% and 91% to 96%, respectively (Kent *et al.*, 2014; Vaegter *et al.*, 2017).

Sociodemographic and clinical characteristics

Patient's characteristics included self-reported sociodemographic and clinical information (sex, age, body weight and height, BMI), highest completed educational level and pain duration in months. BMI was calculated by weight in kilograms divided by height in meters squared (kg/m^2). BMI categories were divided into underweight (BMI <18.5), normal weight (BMI 18.5 to 24.9), overweight (BMI 25.0 to 29.9) and obese (BMI ≥30.0).

Statistical analysis

The sample size calculation was performed a priori and considered a small effect size of 0.2 for a one-way analysis of variance (ANOVA) to detect the between-group difference according to S-TOFHLA classification (adequate, marginal or inadequate health literacy), considering outcomes of pain severity (NPRS) and functional limitation (PSFS). The sample size calculation estimated a total of 243 subjects considering the level of significance of 0.05 and a power of 0.80 and was performed in the G*Power Software version 3.1.9 (Heinrich-Heine-Universität, Düsseldorf, Germany).

The demographic and clinical variables of the study population were summarized descriptively. Categorical variables are presented in absolute frequency and proportion of the sample and continuous variables as means and standard deviation (SD). For continuous variables, the normal distribution of the outcomes was verified by the Shapiro–Wilk test. Due to the parametric distribution, a one-way ANOVA was used to test for between-group differences (adequate, marginal and inadequate health literacy). *Post hoc* Tukey tests were used for multiple comparisons of means when significant F value was found. The interaction of significant variables was investigated by one-way analysis of covariance (ANCOVA) for age and two-way ANOVA for sex. A p-value <0.05 was considered significant for all analyses. The statistical analysis was performed using JASP version 0.10.2.0.

RESULTS

A total of 243 participants were included. One hundred twenty-three (50.62%) participants were classified as adequate health literacy, 24 (9.88%) as marginal health literacy and 96 (39.50%) as inadequate health literacy. Participant characteristics are presented in Table 1.

Comparison of pain-related interference and pain-related distress

A one-way ANOVA showed between-group differences for the kinesiophobia [$F(2, 240) = 6.732$, $p = 0.001$]. A Tukey *post hoc* test revealed that participants with adequate health literacy had lower values of kinesiophobia than the other groups (adequate = 1.53; marginal = 3.79; inadequate = 2.56) (Table 2). A one-way ANCOVA showed between-group differences for the kinesiophobia [$F(2, 239) = 7.920$, $p < 0.001$] and pain severity [$F(2, 239) = 4.555$, $p = 0.011$], whilst controlling for age (Table 2 and Figure 1). A two-way ANOVA revealed no statistically significant interaction between health literacy and sex on the pain-related interference and pain-related distress outcomes (Table 2). Functional limitations and other psychosocial factors demonstrated non-significant results among the groups.

DISCUSSION

The current study compared pain-related interference and pain-related distress in patients with musculoskeletal pain and different levels of health literacy. More than one in three patients recruited from Brazilian public physiotherapy outpatient departments had inadequate levels of health literacy. Regarding pain-related interference, the group with inadequate health literacy presented high values of the pain severity, when controlling for age. In terms of pain-related distress, the low levels

Table 1: Characteristics of the study participants ($n = 243$)

Characteristics	Total, $n = 243$	Adequate health literacy, $n = 123$	Marginal health literacy, $n = 24$	Inadequate health literacy, $n = 96$	p-value
Sex, female, n (%)	191 (78.60%)	83 (67.48%)	21 (87.50%)	87 (90.62%)	<0.001
Age, mean (SD)	55.55 (13.86)	49.17 (14.44)	61.29 (8.73)	62.29 (9.81)	<0.001
Weight (kg), mean (SD)	72.21 (14.59)	75.79 (13.90)	67.20 (10.34)	68.88 (15.31)	<0.001
Height (m), mean (SD)	1.62 (0.97)	1.65 (0.88)	1.59 (0.58)	1.58 (0.99)	<0.001
Body mass index (kg/m^2), n (%)					0.683
Underweight, n (%)	3 (1.23%)	1 (0.81%)	—	2 (2.08%)	—
Normal weight, n (%)	93 (38.27%)	43 (34.95%)	10 (41.66%)	40 (41.66%)	—
Overweight, n (%)	81 (33.33%)	42 (34.14%)	10 (41.66%)	29 (30.20%)	—
Obese, n (%)	66 (27.16%)	37 (30.08%)	4 (16.66%)	25 (26.04%)	—
Highest educational level, n (%)					<0.001
Primary school, n (%)	86 (35.39%)	15 (12.19%)	12 (50.00%)	59 (61.45%)	—
High school, n (%)	97 (39.91%)	57 (46.34%)	9 (37.50%)	31 (32.29%)	—
Undergraduate level, n (%)	53 (21.81%)	44 (35.77%)	3 (15.50%)	6 (6.25%)	—
Graduate level, n (%)	7 (2.88%)	7 (5.70%)	—	—	—
Pain duration (months), mean (SD)	90.7 (104.7)	78.7 (86.3)	93.4 (113.7)	105.4 (121.6)	0.171

SD: standard deviation.

Table 2: Comparison of pain-related interference and pain-related distress among patients with musculoskeletal pain and different levels of health literacy ($n = 243$)

Characteristics	Adequate health literacy, $N = 123$	Marginal health literacy, $N = 24$	Inadequate health literacy, $N = 96$	One-way ANOVA p-value	One-way ANCOVA p-value	Two-way ANOVA p-value
Pain-related interference						
Pain severity, mean (SD)	3.83 (3.27)	3.00 (3.36)	4.63 (3.45)	0.058	0.011	0.994
Patient Specific Functional Scale, mean (SD)	6.21 (1.67)	6.89 (1.71)	6.48 (2.80)	0.325	0.056	0.437
Pain-related distress						
Anxiety, mean (SD)	6.35 (3.11)	6.25 (3.61)	5.59 (3.60)	0.247	0.462	0.353
Social isolation, mean (SD)	1.90 (2.93)	3.08 (3.87)	2.54 (3.63)	0.169	0.453	0.165
Perceived stress, mean (SD)	5.73 (3.38)	4.33 (4.15)	5.65 (3.62)	0.203	0.230	0.082
Catastrophization, mean (SD)	5.05 (3.19)	4.95 (3.97)	3.91 (4.23)	0.073	0.296	0.102
Depression, mean (SD)	3.20 (3.40)	3.91 (3.93)	3.59 (3.68)	0.610	0.126	0.888
Kinesiophobia, mean (SD)	1.53 (2.48)	3.79 (4.05)	2.56 (3.47)	0.001	<0.001	0.744

SD: standard deviation.

of kinesiophobia were described by participants with adequate health literacy. Our findings also revealed no significant difference in functional limitation and other psychosocial factors (anxiety, social isolation, perceived stress, catastrophization and depression) among adequate, marginal and inadequate health literacy groups.

The current findings revealed that pain severity was higher in patients classified as inadequate health literacy than other groups, when controlling for age. Similarly, an association between pain intensity and health literacy after controlling for age and sex was reported in patients with chronic pain (Köppen *et al.*, 2018). Previous studies showed that low levels of health literacy were associated with higher rates of pain intensity (Van Hecke *et al.*, 2016; Köppen *et al.*, 2018). Although the mechanism underlying the relationship between inadequate health literacy and pain intensity remains unclear, previous studies reported insufficient knowledge about pain management and poor coping strategies that influence pain intensity (Devraj *et al.*, 2013; Joplin *et al.*, 2015; Adams

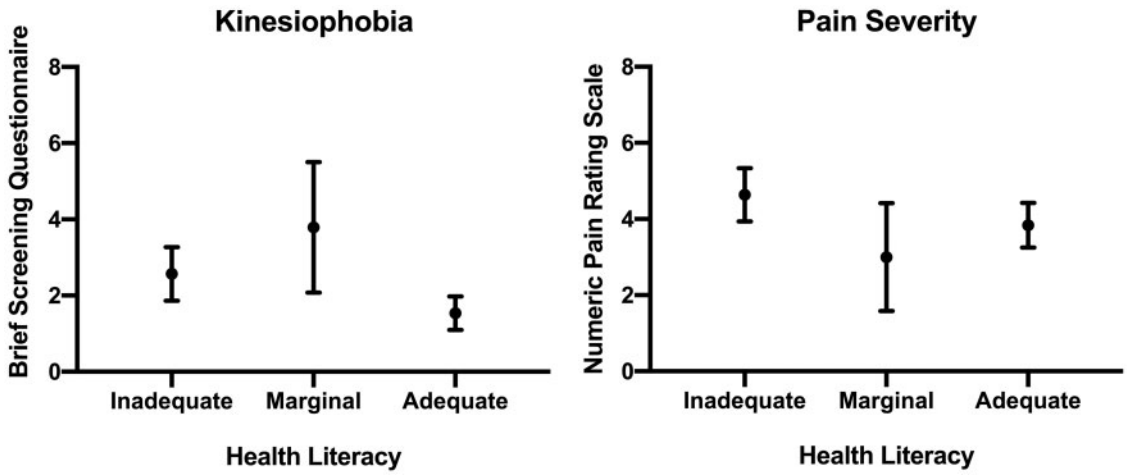

Fig. 1: Comparison of kinesiophobia and pain severity among patients with musculoskeletal pain and different levels of health literacy.

et al., 2016). Additionally, we assumed that the educational level would interact with health literacy and pain intensity. Our findings identified that patients with inadequate health literacy had the lowest level of education, corroborating a prior study (Lacey *et al.*, 2018).

Surprisingly, the level of functional limitation did not differ between groups in the current investigation. There are contradictory findings in the literature regarding functional ability and health literacy. Low or adequate health literacy levels did not significantly correlate with disability in patients with arthritis (Bhat, 2008). Although the causes of functional limitation are diverse, limited health literacy predicted a decline in functional status among older adults (Smith *et al.*, 2015). Similarly, low health literacy was associated with functional limitation in older adults (Kim, 2009). The health condition of the population studied, and the instrument used to measure the functional ability may be crucial to the impact of health literacy on the functional limitation. Self-reported tools are feasible to clinical practice but present several shortcomings (e.g. memory and recall skills) (Winther *et al.*, 2015) and discrepancies between perceptions of the patients (underestimation or overestimation) and their true ability.

Our results revealed that participants with adequate health literacy had lower values of kinesiophobia compared to other groups. Kinesiophobia is associated to educational level (Bilgin *et al.*, 2019). An explanation of our findings might be those patients with adequate health literacy had an educational level superior to the other groups. Thus, the association between kinesiophobia and health literacy may be mediating by the educational level. Individuals with low educational levels are more likely to present low health literacy levels (Stormacq *et al.*, 2019). Also, inadequate health literacy was more prevalent among people without a high school degree than among people with a high school degree (Howard *et al.*, 2006). In Brazil, Maragno *et al.* (Maragno *et al.*, 2019) showed that there were no participants classified as inadequate health literacy who had $\geq$12 schooling years. Finally, the low level of education increases the risk of low health literacy (Van Der Heide *et al.*, 2013). Nevertheless, a previous study showed that there was no significant correlation between educational level, pain self-efficacy and kinesiophobia in patients with subacute and chronic low back pain (Ferrari *et al.*, 2019). Therefore, the relationship between kinesiophobia and health literacy levels may be a particular feature of patients with musculoskeletal pain.

Health literacy levels vary in countries. In India, 77% of the patients presented very low health literacy scores (Rathnakar *et al.*, 2013), in Zambia, 60% of the patients were classified as low health literacy (Schrauben and Wiebe, 2017), in the present study, an inadequate level of health literacy was observed in approximately 40% of patients with musculoskeletal pain. Besides, in Portuguese-speaking adults, approximately 45% of the participants presented inadequate or marginal literacy (Maragno *et al.*, 2019). The development of interventions to support patients with musculoskeletal pain and inadequate health literacy is suggested (Lacey *et al.*, 2018) since there is a substantial burden of low health literacy among people with the

musculoskeletal disease (Hill *et al.*, 2015). Hence, further surveys are needed to evaluate the levels of health literacy in patients with musculoskeletal pain.

Recommendations for future studies

Patients with inadequate health literacy showed high values of kinesiophobia compared to other groups. Also, patients with inadequate health literacy had high values of pain severity when we further controlled for age. This finding provides new insight to clinicians and researchers. Clinicians should be aware of patients with marginal health literacy showed high values of kinesiophobia. Further studies should consider evaluating cognitive factors, such as kinesiophobia between patients with musculoskeletal pain and different levels of health literacy. Health literacy may impact distinctly in specific musculoskeletal condition. Future studies in patients with musculoskeletal pain should be carried out to assess the health literacy considering the clinical diagnoses of the patients. Finally, researchers should use S-THOFLA or instruments with high accuracy to assess the levels of health literacy for the confirmation of the findings of the present study. Future studies should analyse variables as mediators in the relationship between health literacy and functional limitation in patients with musculoskeletal pain.

Strengths and limitations of the study

We recognize the strengths and limitations of the present study. This study is the first to compare pain-related interference and pain-related distress in patients with chronic musculoskeletal pain and different levels of health literacy and used a large sample size. We acknowledge that the cross-sectional design can limit generalizability. However, used a multicentre design to reduce this limitation. Ultimately, we did not anticipate the need for collecting the pain sites in our initial evaluation, nor the specific clinical diagnoses of the patients beyond musculoskeletal pain conditions to be included in this study. We acknowledge that the inclusion of patients with similar clinical diagnoses would be favourable for knowing the impact of health literacy in a homogeneous population. Nonetheless, patients with musculoskeletal pain in different body areas share identical features, and thus common assessments and treatments have been recommended (Lin *et al.*, 2020).

In summary, participants with adequate health literacy showed less kinesiophobia compared to their counterparts. Pain severity had high values in participants with inadequate health literacy, when controlled for age. Functional limitation and other psychosocial factors demonstrated similar results between the three groups of adequate, marginal and inadequate health literacy.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Health Promotion International* online.

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CONFLICT OF INTEREST STATEMENT

The authors state no conflict of interest.

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ORIGINAL ARTICLE

Patients with fibromyalgia present different pain phenotypes compared to patients with generalized pain

Pacientes com fibromialgia apresentam fenótipos de dor diferentes em comparação com pacientes com dor generalizada

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ABSTRACT

BACKGROUND AND OBJECTIVES*:* Fibromyalgia and generalized pain represent a global health problem and are distinct musculoskeletal disorders, but there is an overlap in the clinical presentation between these conditions. However, no study has compared pain characteristics between patients with fibromyalgia and patients with generalized pain. Therefore, the present study aimed to compare pain characteristics and functional limitation of patients with fibromyalgia and patients with generalized pain.

METHODS*:* A pre-planned secondary analysis of data collected from 311 patients with musculoskeletal pain was performed. Pain characteristics included pain intensity, pain duration, pain area, symptoms of central sensitization, presence of neuropathic-like symptoms, and the conditioned pain modulation. The Patient-Specific Functional Scale assessed functional limitation.

RESULTS*:* 98 patients with generalized pain were identified, being 58 (59.18%) classified in the fibromyalgia group and 40 (40.82%) classified in the generalized pain group. Significant differences were found between groups for Widespread Pain Index, Symptom Severity Scale, and Polysymptomatic Distress Scale. Participants with fibromyalgia presented higher values of pain intensity (fibromyalgia = 7.29±2.07, generalized pain = 6.05±2.47; p=0.008), neuropathic-like symptoms (fibromyalgia = 17.74±7.62, generalized pain = 12.17±6.41; p=0.005), and symptoms of central sensitization (fibromyalgia = 51.32±14.26, generalized pain = 33.97±14.65; p<0.001), when compared with generalized pain. There was no significant difference in conditioned pain modulation and functional limitation between groups.

CONCLUSION*:* Patients with fibromyalgia exhibited unfavorable pain characteristics, including pain intensity, neuropathic-like symptoms, and symptoms of central sensitization compared to patients with generalized pain. However, pain duration, functional limitation, and conditioned pain modulation did not present meaningful differences between groups.

Keywords*:* Chronic pain, Fibromyalgia, Pain measurement, Pain threshold.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Fibromialgia e dor generalizada representam um problema de saúde global e são distúrbios musculoesqueléticos distintos, mas há uma sobreposição na apresentação clínica entre essas condições. Entretanto, nenhum estudo comparou as características da dor entre os pacientes com estas condições. Portanto, o presente estudo teve como objetivo comparar as características da dor e a limitação funcional de pacientes com fibromialgia e dor generalizada.

MÉTODOS: Realizou-se uma análise secundária pré-planejada de dados coletados de 311 pacientes com dor musculoesquelética. As características da dor incluíram: intensidade da dor, duração da dor, área da dor, sintomas de sensibilização central, presença de sintomas neuropáticos e a modulação condicionada da dor. A escala de funcionalidade específica do paciente avaliou a limitação funcional.

RESULTADOS: Identificou-se 98 pacientes com dor generalizada, sendo 58 (59,18%) classificados no grupo de fibromialgia e 40 (40,82%) no grupo de dor generalizada. Diferenças significativas foram encontradas entre os grupos para *o* índice de dor generalizada, escala de severidade de sintomas e escala polissintomática de sofrimento. Os participantes com fibromialgia apresentaram maiores valores de intensidade da dor (fibromialgia = 7,29±2,07, dor generalizada = 6,05 ± 2,47; p=0,008), sintomas neuropáticos (fibromialgia = 17,74±7,62, dor generalizada = 12,17 ± 6,41; p=0,005) e sintomas de sensibilização central (fibromialgia = 51,32±14,26, dor generalizada = 33,97±14,65; p<0,001), quando comparados à dor generalizada. Não houve

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diferença significativa na modulação condicionada da dor e na limitação funcional entre os grupos.
CONCLUSÃO*:* Pacientes com fibromialgia exibiram características de dor desfavoráveis, incluindo intensidade de dor, sintomas neuropáticos e sintomas de sensibilização central, quando comparados a pacientes com dor generalizada. Entretanto, a duração da dor, a limitação funcional e a modulação condicionada da dor não apresentaram diferença significativa entre os grupos.
Descritores*:* Dor crônica, Dor musculoesquelética, Fibromialgia, Limiar da dor, Medição da dor.

INTRODUCTION

Fibromyalgia and generalized pain are prevailing in musculoskeletal health conditions. The prevalence of fibromyalgia was 4.7% in Europe[1], 6.4% in the United States[2], 4.4%[3] in Brazil and 2%-3% in the general population[4,5]. The prevalence of chronic widespread pain was 24% in Brazilian women[3], and 10.6%[6], or one in ten individuals, are affected by chronic widespread pain in the general population[6]. Patients with fibromyalgia present widespread musculoskeletal pain, fatigue, sleep disturbances, and cognitive changes[7,8]. Several instruments are available for the assessment of fibromyalgia and generalized pain. Preliminary criteria for the classification of fibromyalgia emerged in 1990[9]. In the last update, a combination of the Widespread Pain Index (WPI), which was designed initially to assess pain distribution[10], the Symptom Severity Scale (SSS), which evaluates cognitive and general somatic symptoms[11], and the combination of WPI and SSS that results in the Polysymptomatic Distress Scale (PSD), which measures the severity of fibromyalgia symptoms, have been recommended as diagnostic criteria[10].
Fibromyalgia and generalized pain are distinct musculoskeletal disorders, but there is an overlap of the clinical presentation between these conditions. Likewise, chronic widespread pain and multisite pain present similar symptoms of fibromyalgia[12]. A previous study claimed that fibromyalgia and chronic widespread pain differ more in quantitative than qualitative measures[13]. Patients with fibromyalgia and generalized pain had higher symptoms of pain, anxiety and depression than those with regional pain[14]. Fibromyalgia patients have more intense and persistent pain than patients with chronic widespread pain[13]. Moreover, fibromyalgia patients had more comorbidities, pain-related drugs, poorer health status, function and sleep, lower productivity, and higher costs compared to patients without chronic widespread pain and with chronic widespread pain but without fibromyalgia[15]. Generalized pain may be associated with fatigue, psychological distress, and concentration problems, like fibromyalgia[7,10]. Still, while the two conditions were similarly disabling[3], fibromyalgia has unfavorable clinical presentation when compared to chronic widespread pain[13,16]. However, the diagnosis of fibromyalgia and generalized pain remains troublesome, many redundancies exist[17] and it is unclear whether the addition of the cognitive and somatic symptoms adds meaningful value to the clinical phenotype of these patients. The identification of particular pain characteristics of these overlapping conditions may contribute to tailored treatment.
Fibromyalgia has distinct pain features when compared to other musculoskeletal conditions. A deficit of endogenous pain inhibitory systems is observed in fibromyalgia but not in chronic low back pain[18]. Patients with fibromyalgia also present higher levels of neuropathic-like symptoms compared to patients with rheumatoid arthritis[19]. Likewise, reduced pain threshold[13,20], increased temporal summation[21], decreased conditioned pain modulation (CPM)[21] and presence of central sensitization have been reported in patients with fibromyalgia[22]. However, no study has compared pain characteristics between patients with fibromyalgia and patients with generalized pain. Therefore, the present study aimed to compare pain characteristics and functional limitation of patients with fibromyalgia and patients with generalized pain. The hypothesis was that patients with fibromyalgia would report more severe symptoms, higher levels of functional limitation and impaired pain modulation in the cold pressor test than patients with generalized pain.

METHODS

A pre-planned secondary analysis of data collected from a previous study by the present group of authors was undertook[23]. The original study was a cross-sectional observational study that followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria (Atachment 1)[24]. The study included 311 patients with musculoskeletal pain to compare the pain characteristics of patients with musculoskeletal pain classified according to PainDETECT as nociceptive pain, unclear and neuropathic-like symptoms. The current study excluded 213 patients with musculoskeletal pain without generalized pain and had a final sample of 98 patients with generalized pain. The original study was approved by the Research Ethics Committee of Federal Institute of Rio de Janeiro (number: 02228818.0.3001.5258), following the Helsinki Declaration for research in humans. All patients who met the eligibility criteria signed the informed consent form before the study procedures.

Study participants

Patients with musculoskeletal pain (aged 18 years and over) who sought treatment in the outpatient physiotherapy clinic of Gaffrée and Guinle University Hospital were enrolled between March and September 2019. The original study included patients with acute pain (pain duration less than three months) and chronic pain (pain duration greater than three months). Musculoskeletal pain was defined as pain perceived in a body region with muscular, ligament, bone, or joint origin[25]. The current study identified patients with generalized pain that could be classified as generalized pain or fibromyalgia according to the 2016 modified American College of Rheumatology (ACR) criteria. The study excluded patients who had a surgical procedure in the spine, pregnant women, patients with rheumatologic diagnosis in the acute inflammatory phase, with tumors, and patients who were illiterate or who could not complete the self-reported questionnaires.

Procedures

Patients were referred for an evaluation consisting of a clinical history and physical examination. Participants completed a

self-report questionnaire that included information on their sociodemographic characteristics (age, gender, weight, height, and body mass index), pain characteristics (pain intensity, pain duration, pain area, symptoms of central sensitization, presence of neuropathic-like symptoms, and CPM), functional limitation, and lifestyle factors (smoking, alcoholism, and physical activity). The completion of all questionnaires was supervised by one of the examiners for clarification, in case of uncertainties. The two examiners involved (J.V.B and M.C.B) had, respectively, two and 32 years of work experience in treating patients with musculoskeletal disorders. The clinical history assessment lasted approximately 10 minutes per participant. Next, patients were referred for evaluation of the efficiency of the CPM.

Patient classification

Fibromyalgia diagnosis was performed using the WPI and the SSS. WPI is a self-reported list of painful regions composed of 19 body areas, and the patient must mark the areas in which he or she felt pain during the last week. Each marked area is equivalent to 1 point. The final score varies between zero and 19 points. SSS is the sum of the severity scores of 3 symptoms (fatigue, waking unrefreshed, and cognitive symptoms) plus the totality of specific symptoms that occurred during the previous 6 months (headaches, pain or cramps in the lower abdomen, and depression). Fibromyalgia diagnosis was confirmed when WPI≥7 and SSS score≥5 or WPI of 4-6 and SSS score≥9, according to the 2016 modified American College of Rheumatology criteria[10]. Fibromyalgia severity was measured by the Polysymptomatic Distress Scale (PDS). The sum of the WPI obtains this scale (zero-19) and the SSS (zero-12) with a final score that varies between zero-31. According to the 2016 modified ACR criteria, a PDS score of at least 12 represents an approximate level of fibromyalgia diagnosis[10]. The psychometric assessment of WPI demonstrated good construct and criterion validity between young patients with painful conditions[26].

Generalized pain was defined when the participant reported pain in at least 4 of 5 regions (upper left and right, lower left and right, and axial) of the WPI. Jaw, chest, and abdominal pain are not included in generalized pain definition[10].

Main outcome measures

Pain intensity was assessed by the numeric pain rating scale (NPRS). The Central Sensitization Inventory (CSI) was used for evaluating symptoms associated with central sensitization. Neuropathic-like symptoms were assessed by the PainDETECT questionnaire[27]. Functional limitation was measured using the Patient-Specific Functional Scale[28] (PSFS). The cold pressor test assessed CPM. All questionnaires and tests were completed on the same day.

Pain characteristics

Pain intensity was measured during the initial evaluation using the NPRS from zero (no pain) to 10 (worst pain possible). Patients were oriented to rate their pain intensity now of the initial evaluation. The duration of pain was recorded in months, and patients were classified with chronic musculoskeletal pain if they had pain for more than three months[29]. Pain area was measured using the WPI. The sum of the WPI (0-19) and the SSS (0-12) results in the polysymptomatic distress (zero-31).

The CSI is an instrument developed to identify patients with symptoms associated with central sensitization[30]. Part A assesses 25 health-related symptoms commonly observed in patients with central sensitivity syndrome. Part A is scored on a 5-point Likert scale from 0 (never) to 4 (always), with a total of 100 points, and higher scores represent an increase in the severity of symptoms.

Part B is not scored and encompasses ten previous diagnoses of an individual, including seven central sensitivity syndromes and three disorders related to central sensitization syndrome. The optimal cut-off point was established at 40/100 in patients with central sensitivity syndrome[31,32]. The severity of symptoms related to central sensitization has been classified into sub-clinical (0–29), mild (30-39), moderate (40-49), severe (50-59) and extreme (60-100)[31,33], where higher scores indicate an increase in the severity of symptoms[34]. The Brazilian version of the CSI demonstrated strong psychometric properties[35].

PainDETECT is a self-administered questionnaire that encompasses four domains as follows: the intensity of pain (three questions), pain course pattern (four graphs), areas of pain and the presence of radiating pain (body chart drawing), and sensory descriptor items of pain (seven questions). For each question, six different answers are possible, with scores from zero (never) to five (very strongly). By summing up the scores given in each domain, a final score between -1 to 38 can be achieved. The PainDETECT is validated for many neuropathic pain conditions. In the last years, it was also validated for the use in mixed pain conditions such as rheumatoid arthritis, osteoarthritis, cancer pain, and lumbar spondylolisthesis. The cut-off points for the original questionnaire indicate that in the scores≤12 a neuropathic component is unlikely, whereas, in the ≥19 scores, a neuropathic component is probable[27,36]. The Brazilian version of PainDETECT is indicated as useful to identify neuropathic components in the pain of Brazilian patients[37].

Functional limitation

Functional limitation was investigated using the PSFS, which is a self-reported measure used to assess functional change in patients with musculoskeletal disorders. Patients should identify up to five important activities they are unable to perform or are restrict because of their pain and classify on an 11-point scale the current level of difficulty associated with each activity. PSFS has easy applicability and can be used clinically as an outcome measure[28,38].

Conditioned pain modulation

Cold pressor test is a psychophysical test used to assess the CPM, where the cold pain is the conditioning stimulus, and pressure

pain threshold (PPT) is the test stimulus. The cold pressor is an appropriate method to assess the descending nociceptive inhibitory system[39]. The conditioning stimulus was the immersion of the participants` hand in a bucket with temperature-controlled cold water (1ºC – 4ºC) monitored by a thermometer (5130 model, Incoterm™, Hong Kong, Sha Tin, China), for up to one minute. The participant was instructed to remain with the hand immersed in water without making muscle contractions or changes in position. The withdrawal of the side from the water was allowed when the patient could no longer tolerate the painful stimulus. Room temperature, humidity, lighting, and noise were maintained constant during the entire procedure.

PPT measurement was performed before and after one minute of the cold pressor test, using a digital pressure algometer (model Force Ten FDX, Wagner Instruments™, Greenwich, CT, USA). The distal part of the dorsal forearm and tibialis anterior muscle, which had not been immersed in water, were chosen to be evaluated due to the lack of relationship with participant's musculoskeletal complaints. The two sites were assessed in the same order for all participants. The operation of the pressure algometer and measurement of PPT were explained to patients before the assessment. In addition, a familiarization procedure was carried out with the pressure algometer by applying pressure to the dominant forearm to ensure that the test had been understood. The force was gradually increased (1 kilogram-force/s) until the feeling of pressure from the primary subject was changed to pain. PPT was recorded in kilograms-force (kgf) when the patient gave the verbal command "pain". The classification of the CPM efficiency was based on the following strategy: evidence of impaired pain modulation in two sites. Only patients with the inefficiency of the CPM in both locations (the anterior tibialis muscle and the distal part of the dorsal forearm) were classified as impaired pain modulation[40]. Upper and lower limb sites were used to avoid the inclusion of the patients with peripheral sensitization according to recommendations for CPM[40]. Also, the efficiency of the CPM was assessed by calculating the difference between PPT values in the cold pressor test (differences between final and initial value). Negative values represented an inefficiency of CPM and null or positive values were considered a typical response of CPM.

Statistical analysis

Demographic and clinical variables of the study population are presented as mean and standard deviation for continuous variables. Categorical variables are presented numerically and as a percentage of the sample. For continuous variables, the normal distribution of the outcomes of the study was verified by the Shapiro-Wilk test. The group of patients who presented fibromyalgia was compared with those with generalized pain. The comparison between groups according to the outcome's measures: the unpaired t-test performed pain intensity and pain duration due to the parametric distribution of the variables. The Chi-Square test was used to compare categorical variables: functional limitation, symptoms of central sensitization, neuropathic-like symptoms, and efficiency of the CPM. A significance level of less than 5% ($p<.05$) was considered for all analyses.

The statistical analysis was performed using JASP version 0.10.2.0. Given the lack of sample size calculation due to the secondary analysis, a post hoc power analysis was performed to determine whether the sample size was large enough for the findings to be statistically valid and to examine the potential for type II errors. The post hoc analysis was performed for estimation of the statistical power of the present study by unpaired t-test using G*Power 3.1.9.4 (Heinrich-Heine-Universität, Düsseldorf, Germany).

RESULTS

A total of 98 participants with generalized pain was identified. Among the included participants, 83 (84.69%) were women. The mean age was of 57.94±11.64 years old, and the mean body mass index was 27.91±6.65 kg/m^2. Forty-two (44.21%) participants reported practicing physical activities. All participants completed the questionnaires and the cold pressor test with no adverse events. Fifty-eight (59.18%) participants were classified with fibromyalgia and 40 (40.82%) participants were classified with generalized pain solely. Patients with fibromyalgia had higher number of pain areas in the WPI [fibromyalgia=11.39±3.52, generalized pain=8.67±3.35; p<0.001; power=0.96], more severe symptoms in the SSS [fibromyalgia=7.96±2.21, generalized pain=4.30±2.27; p<0.001; power =0.99], and in the PDS [fibromyalgia=16.75±5.29, generalized pain=12.97±3.75; p<0.001; power=0.98] than patients with generalized pain (Table 1).

A comparison of pain characteristics and functional limitation between patients classified with fibromyalgia and patients classified with generalized pain is presented in table 2. Participants with fibromyalgia presented higher values of pain intensity [fi-

Table 1. Characteristics of the study participants (n= 98)

Characteristics	Fibromyalgia n=58	Generalized pain n=40	p-value
Gender, n (%), female	52 (89.65%)	31 (77.50%)	0.102
Age, mean (SD)	58.94 (9.43)	56.46 (14.31)	0.305
Weight (kg), mean (SD)	72.59 (12.70)	73.07 (11.72)	0.855
Height (m), mean (SD)	1.61 (0.09)	1.59 (0.09)	0.323
Body mass index (kg/m²), mean (SD)	26.94 (7.30)	29.25 (5.45)	0.113
Physical activity (Yes), n (%)	27 (46.55%)	15 (37.50%)	0.453
WPI (0-19), mean (SD)	11.39 (3.52)	8.67 (3.35)	<0.001

Continue...

Table 1. Characteristics of the study participants (n= 98) – continuation

Characteristics	Fibromyalgia n=58	Generalized pain n=40	p-value
SSS (0-12), mean (SD)	7.96 (2.21)	4.30 (2.27)	<0.001
Headache (Yes), n (%)	47 (81.03%)	20 (50.00%)	0.008
Pain or cramps in lower abdomen (Yes), n (%)	25 (43.10%)	8 (20.00%)	0.017
Depression (Yes), n (%)	40 (68.96%)	8 (20.00%)	<0.001
Fatigue (0-3), mean (SD)	2.24 (0.94)	1.25 (0.96)	<0.001
Waking unrefreshed (0-3), mean (SD)	1.94 (1.16)	1.22 (1.20)	0.004
Cognitive symptoms (0-3), mean (SD)	1.84 (1.18)	0.90 (0.95)	<0.001
PDS (0-31), mean (SD)	19.36 (4.60)	12.97 (3.75)	<0.001

SD = standard deviation; WPI = Widespread Pain Index; SSS = Symptom Severity Scale; PDS = Polysymptomatic Distress Scale.

Note: The Student's t-test was used for continuous variables, and the Chi-Square test was used to compare categorical variables.

Table 2. Comparison of pain characteristics and functional limitation between patients with fibromyalgia and patients with generalized pain

Characteristics	Fibromyalgia n=58	Generalized pain n=40	p-value
Pain intensity, mean (SD)	7.29 (2.07)	6.05 (2.47)	0.008
Pain duration (months), mean (SD)	110.17 (116.35)	86.54 (98.54)	0.318
PainDETECT questionnaire, mean (SD)	17.74 (7.62)	12.17 (6.41)	0.005
Nociceptive pain (≤12), n (%)	13 (22.41%)	20 (51.28%)	0.003
Unlikely (13-18), n (%)	19 (32.75%)	12 (30.76%)	0.836
Neuropathic pain (≥19), n (%)	26 (44.82%)	7 (17.94%)	0.006
CSI, mean (SD)	51.32 (14.26)	33.97 (14.65)	<.001
Sub-clinical (0–29), n (%)	3 (5.17%)	18 (45.00%)	<.001
Mild (30–39), n (%)	11 (18.96%)	7 (17.50%)	0.855
Moderate (40–49), n (%)	15 (25.86%)	9 (22.50%)	0.705
Severe (50–59), n (%)	8 (13.79%)	4 (10.00%)	0.576
Extreme (60–100), n (%)	21 (36.20%)	2 (5.00%)	<.001
PSFS, mean (SD)	7.75 (2.04)	7.16 (1.91)	0.131
CPM (impaired), n (%)	14 (24.13%)	9 (22.50%)	0.851

SD = standard deviation; CSI = Central Sensitization Inventory; PSFS = Patient Specific Functional Scale;CPM = conditioned pain modulation.

Note: Student's t-test was used for continuous variables, and Chi-Square test was used to compare categorical variables.

bromyalgia=7.29±2.07, generalized pain=6.05±2.47; p=0.008; power=0.74], and pain duration [fibromyalgia=110.17±116.35, generalized pain=86.54±98.54; p=0.318; power=0.17]. Twenty-six (44.82%) participants of the fibromyalgia group and seven (17.94%) participants of the generalized pain group were classified with neuropathic-like symptoms. In the CSI, 44 (75.86%) participants with fibromyalgia and 15 (37.50%) participants of the generalized pain group had scores≥40. Diagnosis of depression was reported by 40 (68.96%) and 8 (20.00%) patients with fibromyalgia and generalized pain, respectively. There was no significant difference in CPM between groups [fibromyalgia=14 (24.13%), generalized pain=9 (22.50%); p=0.851; power=0.855] (Table 2).

DISCUSSION

The present findings confirmed the hypothesis and revealed that participants with fibromyalgia presented more severe symptomatology compared to generalized pain. Pain intensity, symptoms of neuropathic pain and central sensitization were more pronounced in participants with fibromyalgia than in participants with generalized pain. Recognizing that fibromyalgia and generalized pain are distinct musculoskeletal conditions highlights the need for specific treatment. The symptom severity scale has a notable role in the identification of these two conditions.

It is important to recognize the strengths and limitations of the present study. Firstly, to the best of the authors' knowledge, this is the first study that compared the clinical features of patients with fibromyalgia and patients with generalized pain. Second, the recent criteria defined by the ACR for the diagnosis of fibromyalgia and generalized pain was used[10]. Alternative approach to the diagnosis of fibromyalgia has been described despite the lack of measurement properties assessment[41]. Different diagnosis criteria could likely lead to additional findings. Third, the study design implemented many methods to minimize the risk of bias, following current guidelines for this type of study.

Regarding the limitations of the study, the main one is the relatively small number of participants included. Second, there is a lack of objective markers to diagnosis the two health conditions and other comorbidities. Moreover, chronic pain features may be reported dissimilarly using the questionnaire survey or interview survey method[42].

In comparison to patients with generalized pain, patients with fibromyalgia evidenced more impaired pain characteristics, corroborating previous studies[13,16,43]. In the same way, patients with fibromyalgia diagnosis or people whose symptoms met criteria for fibromyalgia had a greater symptom impact than people with chronic pain[44]. The present results showed that pain intensity was higher in patients with fibromyalgia compared to generalized pain. However, the findings revealed that pain duration showed no difference between the groups. On the other hand, patients with fibromyalgia in several studies have reported more intense and persistent pain than patients with chronic widespread pain[13,45-47].

The current study revealed that patients with fibromyalgia presented neuropathic-like symptoms measured by the PainDETECT questionnaire and higher levels of symptoms of central sensitization compared to patients with generalized pain. Likewise, other authors found neuropathic-like symptoms in 67% of patients with fibromyalgia using the PainDETECT questionnaire[19]. According to authors, abnormal wind-up and central sensitization have been reported in patients with fibromyalgia, which also relate to central pain processing abnormalities[22].

Interestingly, the level of functional limitation was similar between the patients with fibromyalgia and patients with generalized pain in the current study. There is evidence that patients with fibromyalgia and widespread pain were considered similarly disabling[3]. However, authors showed that participants with fibromyalgia had more pronounced pain-related interference in function and consequences for daily life compared to patients with chronic widespread pain[47]. The lack of difference in functional limitation between groups may be related to identical demographic and lifestyle features (gender, age, weight, height, body mass index and physical activity) of the participants. Furthermore, both groups had equivalent physical activity behavior. Individuals with chronic widespread pain with poor physical health and coping response to symptoms were identified as non-engagers of physical activity[48].

The present study's findings revealed that there are no significant differences in CPM between groups. Likewise, a previous study showed that patients with chronic widespread pain and fibromyalgia syndrome have equal CPM impairment[49]. On the other hand, a systematic review indicated that CPM seems to be dysfunctional in patients with chronic conditions, such as fibromyalgia[50]. It has been advocated that fibromyalgia syndrome is a condition that revealed clearly CPM impairment[18,51].

Authors showed that there was a deficit of endogenous pain inhibitory systems in fibromyalgia but not in chronic low back pain[18]. Similarly, a study showed that impairment in inhibitory pain modulation scores are likely antecedents to chronic widespread pain[52]. Although several studies observed the impairment in inhibitory pain modulation in participants with fibromyalgia and generalized pain, authors showed that results do not support the idea that a general deficiency of central inhibitory mechanisms is a result of fibromyalgia[53].

Future research in fibromyalgia and generalized pain must emphasize the use of the SSS as a clinical instrument for diagnosis that facilitates the distinction of these conditions. Although patients with fibromyalgia have generalized pain, clinicians must be aware that fibromyalgia and generalized pain are not the same conditions, and thus they may require specific treatments. The presence of more severe symptomatology in patients with fibromyalgia reveals a need for appropriate therapeutic interventions for an assertive treatment for these patients.

CONCLUSION

Patients classified in the fibromyalgia group exhibited higher levels of pain intensity, neuropathic-like symptoms, and symptoms of central sensitization compared to patients with generalized pain. Functional limitation and CPM demonstrated similar results between the two groups. Further studies should investigate the features of patients with fibromyalgia and generalized pain to facilitate the decision making of the clinicians.

AUTHORS' CONTRIBUTIONS

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Statistical analysis, Funding acquisition, Data Collection, Conceptualization, Resource Management, Project Management, Research, Methodology, Writing - Preparation of the original, Writing - Review and Editing, Software, Supervision, Validation, Visualization

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Atachment 1. STROBE Checklist of items that should be included in reports of cross-sectional studies

	Item nº	Recommendation	Page nº
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	01-02
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	01-03
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	03-04
Objectives	3	State specific objectives, including any prespecified hypotheses	05
Methods			
Study design	4	Present key elements of study design early in the paper	05
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	07
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	07
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	09-13
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	09-13
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	NA
		(b) Describe any methods used to examine subgroups and interactions	NA
		(c) Explain how missing data were addressed	NA
		(d) If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	14
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14-16
		(b) Indicate number of participants with missing data for each variable of interest	14-16
Outcome data	15*	Report numbers of outcome events or summary measures	14-16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13
		(b) Report category boundaries when continuous variables were categorized	14-16
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarize key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-19
Generalizability	21	Discuss the generalizability (external validity) of the study results	16-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org. *Give information separately for exposed and unexposed groups.

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ORIGINAL ARTICLE

Relationship between the Widespread Pain Index and the PainMAP software for pain sites measurement in patients with Widespread Pain

Relação entre o Índice de Dor Espalhada e o software PainMAP para medida de localização da dor em pacientes com dor espalhada

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ABSTRACT

BACKGROUND AND OBJECTIVES: Identifying pain sites is essential to managing patients with Widespread Pain. Several instruments have been developed, including pain drawings, a grid system and computerized methods. However, it is not yet known whether the Widespread Pain Index matches an automated method (painMAP) for quantifying the number of pain areas. Therefore, this study aimed to identify the relationship between the Widespread Pain Index and the painMAP software to measure pain sites in participants with Widespread Pain.

METHODS: A pre-planned secondary analysis of data collected from 311 patients with musculoskeletal pain was conducted. The Widespread Pain Index and the painMAP software assessed pain sites. Spearman's correlation coefficient investigated the correlation between the Widespread Pain Index and the painMAP software.

RESULTS: A total of 98 participants with Widespread Pain were included in this study. Most participants were female (67; 83.7%), with a mean age of 57,7±11,5 years, mean height of 1.6 (0.1) meters and mean weight of 73.2 (11.8) kilograms. The mean pain intensity was 6.7 (2.0), and the pain duration was 92.3 (96.3) months. The mean number of pain sites in the Widespread Pain Index was 10.1 (3.7), and in the painMAP software, it was 11.7 (8.8). A weak positive correlation (rho = 0.26, 95% CI 0.45 to 0.04, p = 0.022) between the Widespread Pain Index and the painMAP software was found.

CONCLUSION: The Widespread Pain Index and the painMAP software showed a weak correlation for assessing pain sites in participants with Widespread Pain.

Keywords: Chronic Pain, Fibromyalgia, Pain management, Pain measurement.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A identificação dos locais de dor é um aspecto essencial no manejo de pacientes com Dor Espalhada. Vários instrumentos foram desenvolvidos, incluindo desenhos de dor, um sistema de grade e métodos computadorizados. No entanto, ainda não se sabe se o Índice de Dor Espalhada coincide com um método automatizado (painMAP) para quantificar o número de áreas de dor. Portanto, este estudo teve como objetivo identificar a relação entre o Índice de Dor Espalhada e o *painMAP* para medir as áreas doloridas em participantes com esse quadro de dor.

MÉTODOS: Uma análise secundária pré-planejada de dados coletados de 311 pacientes com dor musculoesquelética foi realizada. O Índice de Dor Espalhada e o *painMAP* avaliaram as áreas de dor. O coeficiente de correlação de Spearman foi utilizado para investigar a correlação entre o Índice de Dor Espalhada e o *software painMAP*.

RESULTADOS: Um total de 98 participantes com Dor Espalhada foram incluídos neste estudo. A maioria dos participantes era do sexo feminino (67;83,7%), com média de idade de 57,7±11,5 anos, média de altura de 1,6 (0,1) metros e média de peso de 73,2 (11,8) quilogramas. A média de intensidade da dor foi de 6,7 (2,0) e da duração da dor de 92,3 (96,3) meses. O número médio de áreas de dor no Índice de Dor Espalhada foi de 10,1(3,7) e no *software painMAP* foi de 11,7 (8,8). Uma correlação positiva fraca (rho=0,26, IC de 95% 0,45-0,04, p=0,022) entre o Índice de Dor Espalhada e o *painMAP* foi encontrada.

CONCLUSÃO: O Índice de Dor Espalhada e o *painMAP* mostraram correlação positiva fraca para avaliar as áreas de dor em participantes com dor espalhada.

Descritores: Dor Crônica, Fibromialgia, Manejo da dor, Medição da Dor.

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INTRODUCTION

Musculoskeletal health conditions are a common cause of pain in the general population. Patients with musculoskeletal pain (MP) commonly present pain in more than one body region[1,2]. Chronic Widespread Pain (CWP) can be classified as chronic primary pain (i.e., pain in one or more body regions that persists or recurs for longer than three months and is associated with significant emotional distress or that cannot be better accounted for by another chronic pain condition)[3]. In the general population, one in every 10 adults had CWP[4], accounting for about 46% of all outpatient consultations in Europe[5,6]. In Brazil, 24% of the women had CWP[7]. Multiple pain sites have been associated with increased pain severity[8,9], restricted activities of daily living[2], reduced quality of life[8,9], and poor prognosis regardless of treatments[10]. Thus, identifying Widespread Pain (WP) patients is crucial to assist clinicians and researchers in offering appropriate treatment approaches.

Several instruments are available for the assessment of pain distribution. The pain drawing is one of the health professionals' strategies most used to quantify pain distribution[11,12]. Several studies related to the reliability of measuring pain distribution and location use the pain drawing[13-19]. The total area of the body in pain and the pain's anatomical location is commonly measured by clinicians and researchers[13]. A grid system[20] and computerized assessment score the pain sites[11,12,19]. Although the evaluation of pain sites can be performed by reliable and valid instruments such as ImageJ software[12], it is worth noting that these instruments are challenging for participants to complete and represent a time-consuming evaluation for clinicians.

Instruments chosen by clinicians and researchers to assess pain sites should be simple, easy, fast, and low-cost. In this sense, the Widespread Pain Index (WPI) was designed to evaluate pain distribution according to the number of reported painful body regions. WPI is a self-reported list of painful sites composed of 19 body areas[21] and demonstrated good construct and criterion validity between young patients with painful conditions[22]. WPI is a clear, well-organized and low-cost instrument compared to the Regional Pain Scale[23] and the Self-Assessment Pain Scale[24] to determine pain sites. WPI has been used in patients with chronic pain[25,26], surgical samples[27], and young individuals with painful conditions[22].

However, WPI can be confusing for participants who are not used to the terminologies of body site instruments, with a body chart likely to assist the participant in visualizing pain sites. On the other hand, the painMAP software was developed to quantify the number of pain sites and areas, with excellent inter and intra-rater reliability in patients with low back pain[19]. No study has evaluated the correlation between WPI and a computerized method to assess pain sites. Therefore, the present study aimed to identify the relationship between the WPI and the painMAP software for measuring pain sites in participants with WP. The present study hypothesized that painMAP would positively correlate to WPI for measuring pain sites in participants with WP.

METHODS

The present study undertook a pre-planned secondary analysis of data collected from a previous study by this same group[28]. The current study is a cross-sectional study following the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) requirements[29]. Similarly, the original research was cross-sectional and followed the STROBE criteria[29]. The original study included 311 participants with MP to compare the pain characteristics according to the painDETECT questionnaire classification as nociceptive pain, unclear and neuropathic-like symptoms[28]. The original study included participants with MP (aged 18 years and over), with acute pain (pain duration less than three months) and chronic pain (pain duration greater than three months). MP was defined as pain perceived in a region of the body with muscular, ligament, bone, or joint origin. The original study excluded participants who had a surgical procedure on the spine, pregnant women, patients with rheumatologic diagnosis in the acute inflammatory phase, tumors, were illiterate, or could not complete the self-reported questionnaires.

The current study excluded 213 participants with MP without WP and had a final sample of 98 patients with WP. The original study was approved by the Research Ethics Committee of the Federal Institute of Rio de Janeiro (number: 02228818.0.3001.5258) following the Helsinki Declaration for research in humans. All patients met the eligibility criteria and signed the Free and Informed Consent Term (FICT) form before the study procedures.

Study Participants

Consecutive participants with WP (aged 18 years and over) from two outpatient Physical Therapy departments (Gaffrée and Guinle University Hospital and Augusto Motta University Center), two private clinics, and an outpatient multidisciplinary rehabilitation department (Cabo Frio Rehabilitation Center) in Rio de Janeiro State, Brazil, were enrolled when they sought treatment between March and September 2019. The study included participants with WP (n=98). Of these, 18 participants were excluded because they had painted the area with red and blue pens (n=11), only blue pens (n=2), for not respecting the borders of the body charts (n=1) or for not having pain sites recognized by the painMAP software (n=4).

Therefore, 80 participants with WP were included. Even though the terminology "generalized pain" has been extensively used[21], this research chose WP, following the recent classification of chronic pain for the International Classification of Diseases (ICD-11)[30]. Widespread Pain was defined when the participant reported pain in at least 4 of 5 regions (left and right upper, left and right lower, and axial) in the WPI. Jaw, chest, and abdominal pain are not included in the WP definition[21]. Participants who had a surgical procedure on the spine in the last year, pregnant women, participants with rheumatologic diagnoses in the acute inflammatory phase, with tumors, that were illiterate, or

could not complete the self-reported questionnaires were excluded from the study.

Procedures

Participants were referred for an initial evaluation of the clinical history and physical examination. The WPI assessed pain sites at the time of assessment. Subsequently, an examiner using the painMAP software calculated the number of pain sites and areas.

Outcomes measures

WPI is a self-reported list of painful regions composed of 19 body areas, and participants must mark the areas in which they felt pain during the last week. Each marked area is equivalent to 1 point. The final score varies between zero and 19 points. The American College of Rheumatology criteria recognizes that a participant had WP when the participant reported pain in at least 4 of 5 regions (left and right upper, left and right lower, and axial) in the WPI. Jaw, chest, and abdominal pain are not included in the WP definition[21]. The psychometric assessment of the WPI demonstrated good construct and criterion validity between young patients with painful conditions[22].

The PainMAP software is a tool for automated image processing for quantifying the number of pain sites and the area from pain drawings in digitized body charts. The painMAP software processes the digitized body charts in image calibration and object detection without any input from the user[19]. The body chart consisted of a 10 x 10 cm (head to feet distance: 6.7 cm) print image containing two views (anterior and posterior), as illustrated in figure 1.

Participants were requested to identify painful areas on the body chart using a red pen during the clinical assessment (Figure 2). Pain drawings were excluded from the study if the participant had not filled in the body area correctly (i.e., had painted the area with red and blue pens or only blue pens or had not respected the borders of the body charts). The validity of the shaded pain sites and the exclusions were assessed by an examiner (JVB) with four years of work experience in treating patients with MP. For a pragmatic assessment, all body charts were photographed once by an examiner (JVB) using one smartphone (Motorola G5). For offline analysis, all digitized images were stored as JPEG files (resolution set to 72 DPI).

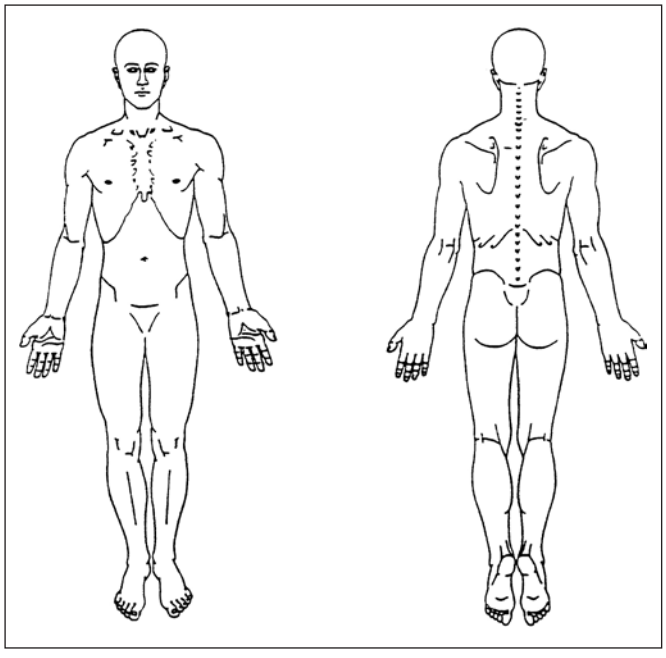

Figure 1. Body chart (10 x 10 cm).

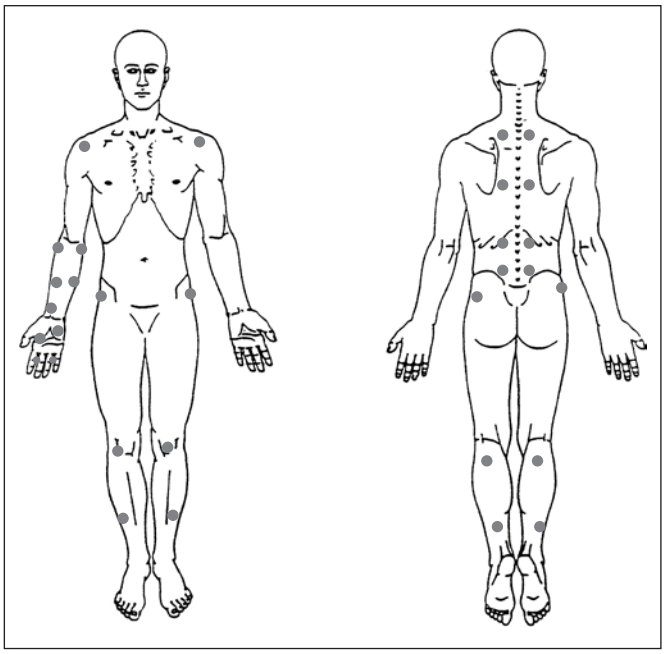

Figure 2. Examples of a body map photo of a participant with chronic Widespread Pain.

Sample size calculation

Sample size calculations assumed a two-sided correlation test, a type I error rate of 0.05 (5%) and 95% of power, taking the pain sites as the unit of analysis. In addition, a minimum Pearson's correlation coefficient of 0.4 between WPI and painMAP software for the pain sites was chosen to determine a sufficient sample size. Therefore, a total of 75 participants with WP was necessary. Ninety-eight participants with WP were recruited, assuming potential data loss. The sample size calculation was performed *a priori* in the G*Power software version 3.1.9.4 (Heinrich-Heine-Universität, Düsseldorf, Germany).

Statistical analysis

The demographic (age, gender, weight and height) and clinical variables (pain intensity and pain duration) of the study participants were summarized descriptively. Paired samples t-tests were used to compare the mean differences between WPI and painMAP software. Categorical variables are presented in absolute frequency and proportion of the sample, and continuous variables as means and standard deviation (SD). For continuous variables, the normal distribution of the outcomes was verified by the Shapiro-Wilk test.

Due to the non-normal distribution of data, the Spearman correlation was used. Spearman's correlations (rho) assessed the relationship between the WPI and the painMAP software. Rho < 0.30 was interpreted as a weak correlation, from 0.30 to 0.60 as a moderate correlation, and ≥ 0.60 as a good correlation[31]. Outliers were excluded by the ROUT method with Q = 1.0%[32]. Statistical evidence of significance level was set to less than 5% for all analyses. Statistical analysis was performed using JASP (version 0.16.1) and Prism for Macintosh, Version 8 (GraphPad Software Inc., San Diego, CA).

RESULTS

Characteristics of the participants

Eight participants with WP were enrolled in this study, 67 (83.7%) females, with a mean age of 57.7 (11.5) years, mean body height of 1.6 (0.1) meters, mean weight of 73.2 (11.8) kg, mean body mass index of 27.6 (6.8) kg/m^2. More than half (56.9%) of participants with WP reported primary school as their highest educational level, 20.2% reported high school, and 18.9% reported undergraduate-level education. Regarding pain characteristics, the mean pain intensity at the moment was 6.7 (2.3) out of 10, the strongest pain level in the last 4 weeks was 8.3 (2.0) out of 10, pain level on average in the previous 4 weeks was 7.3 (2.0) out of 10, and pain duration 92.4 (96.3) months. Moreover, 71 (88.7%) participants with WP were classified with chronic WP, 6 (7.5%) were classified with acute WP, and 3 (3.7%) did not report the duration of their pain.

Table 1. Characteristics of the study participants (n = 80)

Variables	Values (n= 80)
Age (years), mean (SD)	57.7 (11.5)
Height (meters), mean (SD)	1.6 (0.1)
Weight (kg), mean (SD)	73.2 (11.8)
Body mass index (kg/m^2), mean (SD)	27.7 (6.8)
Highest educational level, n (%)	
Primary school, n (%)	45 (56.9)
High school, n (%)	16 (20.2)
Undergraduate level, n (%)	15 (18.9)
Not declare, n (%)	3 (3.7)
Missing, n (%)	1 (0.3)
Pain characteristics	
Pain intensity, mean (SD)	6.7 (2.0)
Pain duration (months), mean (SD)	92.4 (96.3)
Chronic pain, n (%)	71 (88.7)
Number of pain sites (WPI), mean (SD)	10.2 (3.7)
Distribution of painful sites, n (%)	
Neck	59 (73.7)
Upper back	65 (81.2)
Low back	65 (81.2)
Left shoulder	60 (75.0)
Right shoulder	65 (81.2)
Left Upper arm	43 (53.7)
Right Upper arm	43 (53.7)
Left Lower arm	26 (32.5)
Right Lower arm	26 (32.5)
Left hip	53 (66.2)
Right hip	55 (68.7)
Left Upper leg	35 (43.7)
Right Upper leg	37 (46.2)
Left Lower leg	51 (63.7)
Right Lower leg	50 (62.5)
Number of pain sites (painMAP software), mean (SD)	11.7 (8.8)
Pain area (painMAP software), mean (SD)	0.86 (1.1)

Continuous variables are expressed in mean (standard deviation) and categorical variables in absolute (frequency).

The results of the pain sites analysis reported by the participants with WP revealed that the mean number of pain sites in WPI was 10.2 (3.7); the most marked regions in WPI was: upper back (81.2%), lower back (81.2%), right shoulder (81.2%), neck (73.7%), right hip (68.7%), left hip (66.2%), left lower leg (63.7%), right lower leg (62. 5%), and left and right upper arms (53.7%). Data from the painMAP software showed that the mean number of pain sites marked by participants was 11.7 (8.8), and the mean pain area in painMAP software was 0.8 (1.1). Furthermore, paired samples t-test showed there was no significant difference between the mean pain sites marked in the WPI 10.2 (3.7) and the mean pain sites observed in the painMAP software were 11.7 (8.8) (W = 1316.500; z = -0.758; p = 0.449) (Table 1).

A Spearman's correlation coefficient analysis showed a weak positive correlation between WPI and painMAP software for identifying pain sites in participants with WP (rho = 0.26, 95%CI 0.45 to 0.04, p = 0.022) (Figure 3).

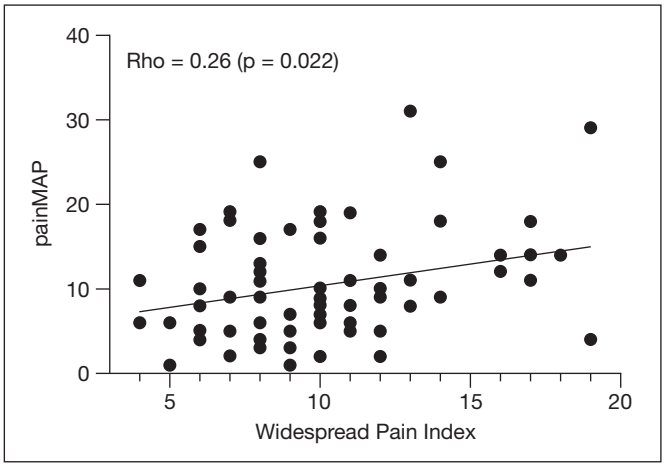

Figure 3. Correlation between the WPI and painMAP software

DISCUSSION

The present study presented a relationship between the number of pain sites in the WPI and painMAP software in patients with WP. Comparing both instruments concerning the mean number of pain sites, similar results were found both in the WPI and in the painMAP software. However, the results of this study found a weak correlation between WPI and painMAP

software for the number of pain sites. Pain drawings are often used in clinical practice to clarify the number of pain sites. Although establish the number of pain sites is necessary, healthcare professionals should consider other relevant information when caring for patients with WP. For instance, painMAP software can provide a total pain area that cannot find in a simple pain drawing.

Regarding the strengths and limitations, this study is the first that assessed the relationship between WPI and computerized methods to determine the pain sites in patients with WP. Secondly, the painMAP software is more detailed compared to the WPI (e.g., while WPI recognizes the left upper arm region only, the painMAP software can identify some regions in the left upper arm, such as anterior and posterior, medial and lateral, proximal and distal). Thirdly, automated downloadable software (i.e., painMAP) can facilitate clinical use. Moreover, the painMAP software is a resource easy to use and does not require user input for image processing/analysis, a specialist and not require much training for image inspection.

Regarding the limitations of the study, the main one is that there is no gold-standard instrument for identifying pain sites. Secondly, the clinical diagnosis of the patients included was not controlled and may affect pain site response. Also, caution is needed with the generalisability of the findings because the results of this research should be tested in different populations. Therefore, further studies that include samples with more patients with other conditions are needed. Finally, precise instruction is required to properly guide participants in completing the body map, since the painMAP software could incorrectly consider painted areas (for instance, outside the body map).

The findings of this research showed a weak correlation between the two methods, contradicting a prior study that reported a strong correlation between similar pain measures[33]. Another study demonstrated that a greater number of pain sites in WPI was associated with a greater number of pain sites on the body diagram ($r=0.57$, $p<0.001$) in young patients with painful conditions[22]. Similarly, there is a strong relationship between the painMAP software and ImageJ software for the number of pain sites ($R^2=0.985$) and pain areas ($R^2=0.952$) domains in body charts of patients with low back pain[19].

The health condition studied (i.e., WP) could have interfered with the findings of this research due to the nature of the high number of pain sites reported by each participant. Arguably, a more localized pain (e.g., knee osteoarthritis) may present a stronger correlation between the instruments (WPI and painMAP software). Additionally, both devices measure painful regions but using a distinct manner. For instance, a body region marked in WPI may have more than one tag in painMAP software. Furthermore, the WPI does not display options for particular areas such as the wrist, ankle, and foot. Therefore, categorizing pain sites using WPI likely loses information and underestimates pain assessment in patients with WP.

Evidence suggests that patients with chronic pain can present distorted body image (i.e., tend to perceive their painful area of the body as increased or reduced)[34-37]. The body image was negatively related to the intensity of pain in men suffering from chronic pain (i.e., rheumatoid arthritis and low back pain)[38]. Patients with chronic low back pain had a more negative body image than patients with subacute low back pain and healthy control group subjects[39]. Moreover, chronic WP patients reported significantly more comorbidities and psychosomatic symptoms than patients with local chronic low back pain[40]a common type of CLP, in primary care settings. METHODS: Fifty-eight German general practitioners (GPs. Arguably, patients with chronic pain conditions present several impairments that may alter the body pain drawings.

Clinicians should be aware of using other computerized methods which can provide valuable information beyond the number of pain sites. Future research must evaluate the relationship between different approaches to assessing pain sites and areas. Pain measurements have been extensively used in WP, but many aspects could be improved in the measurement properties. For instance, pain intensity measures have low or very low-quality evidence for content validity in patients with low back pain, and there is no instrument with superior measurement properties[41].

CONCLUSION

WPI and painMAP software showed a weak correlation in assessing the number of pain sites in patients with WP.

AUTHORS' CONTRIBUTIONS

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Original article

Exploratory analysis of 5 supervised machine learning models for predicting the efficacy of the endogenous pain inhibitory pathway in patients with musculoskeletal pain

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ABSTRACT

Objectives: The identification of factors that influence the efficacy of endogenous pain inhibitory pathways remains challenging due to different protocols and populations. We explored five machine learning (ML) models to estimate the Conditioned Pain Modulation (CPM) efficacy.
Design: Exploratory, cross-sectional design.
Setting and Participants: This study was conducted in an outpatient setting and included 311 patients with musculoskeletal pain.
Methods: Data collection included sociodemographic, lifestyle, and clinical characteristics. CPM efficacy was calculated by comparing the pressure pain thresholds before and after patients submerged their non-dominant hand in a bucket of cold water (cold-pressure test) (1–4 °C). We developed five ML models: decision tree, random forest, gradient-boosted trees, logistic regression, and support vector machine.
Main outcome measures: Model performance were assessed using receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, precision, recall, F1-score, and the Matthews Correlation Coefficient (MCC). To interpret and explain the predictions, we used SHapley Additive explanation values and Local Interpretable Model-Agnostic Explanations.
Results: The XGBoost model presented the highest performance with an accuracy of 0.81 (95% CI = 0.73 to 0.89), F1 score of 0.80 (95% CI = 0.74 to 0.87), AUC of 0.81 (95% CI: 0.74 to 0.88), MCC of 0.61, and Kappa of 0.61. The model was influenced by duration of pain, fatigue, physical activity, and the number of painful areas.
Conclusions: XGBoost showed potential in predicting the CPM efficacy in patients with musculoskeletal pain on our dataset. Further research is needed to ensure the external validity and clinical utility of this model.

1. Introduction

Musculoskeletal pain can be considered an important cause of global disability burden (Vos et al., 2020). In recent years, attention has been focused on the potential role of central nociceptive pathway dysfunction in the spread of pain and hyperalgesia in different pain conditions (Arendt-Nielsen et al., 2015; Arendt-nielsen et al., 2018; Ossipov et al., 2014; Wang et al., 2013). Altered central pain modulation involves impaired modulatory mechanisms within the central nervous system whereby nociceptive pathways are less inhibited and nociceptive facilitatory pathways are enhanced, resulting in the augmentation of nociceptive transmission (Baert et al., 2016). In humans, the endogenous pain inhibitory pathways can be experimentally assessed by using the concept of "pain inhibits pain", in which one painful stimulus (i.e., the conditioning stimulus), modulates another pain-inducing stimulus (i.e., the test stimulus) in a psychophysical paradigm called the conditioned

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pain modulation (CPM) paradigm (Yarnitsky et al., 2015).

CPM has been considered a useful measure as part of quantitative sensory testing (Ramaswamy and Wodehouse, 2021). Quantitative sensory testing is considered a one potential method for assessing the mechanisms that contribute to the development and/or maintenance of chronic pain (Cruz-Almeida and Fillingim, 2014). Recent evidence suggests that quantitative sensory testing can predict worse musculoskeletal pain and disability outcomes (Georgopoulos et al., 2019; Dürsteler et al., 2021). The cold pressor test is an appropriate and a recommended method for assessing endogenous pain inhibitory pathways (Yarnitsky et al., 2015; Lewis et al., 2012a). The combination of pressure pain threshold induced by pressure algometry and the cold pressor test provided the most reliable CPM effect compared with heat pain, electrical pain, single-point pressure pain thresholds, cuff-induced pain detection, and tolerance thresholds (Imai et al., 2016). However, the current literature provides insufficient and conflicting evidence on the influence of personal and clinical factors on CPM (Clark et al., 2017). Previous studies have shown that the efficacy of CPM can be influenced by various factors such as sex, age, stress, physical activity, perceived pain, and attentional focus on the conditioning stimulus. However, the impact of these factors may vary depending on the testing location and methodology (Mertens et al., 2021). Generally, men exhibit more efficient CPM compared to women (Popescu et al., 2010), and older individuals may have reduced inhibitory responses compared to younger individuals (Grashorn et al., 2013; Lewis et al., 2012b), although some studies have reported no age-related effect on CPM efficacy (Skovbjerg et al., 2017). Therefore, further investigation into the factors that affect CPM efficiency is necessary to enhance our comprehension of this phenomenon and its clinical implications.

The application of machine learning (ML) in healthcare has gained significant attention, driven by its ability to provide valuable decision support information to healthcare professionals (Choudhury et al., 2020; Maffulli et al., 2020; Miles et al., 2020; Nindrea et al., 2018). In addition, explainability methods enable explorative research approaches in complex datasets to identify relevant aspects of a model, leading to insights that can be utilized in future studies or in clinical practice (Lötsch and Ultsch, 2018). This study aimed to develop and explore five machine learning predictive models capable of estimating the efficiency of endogenous pain inhibitory pathways in patients with musculoskeletal pain from one CPM experimental design. We used a dataset from "real-life" patients with musculoskeletal pain to develop five supervised learning algorithms: decision tree, random forest, XGBoost, logistic regression and support vector machine. Second, we identified the variables that exert the most significant influence on the efficiency of the endogenous pain inhibitory system.

2. Methods

2.1. Study design and ethical considerations

This is a secondary analysis of a cross-sectional study (Bezerra et al., 2021) approved by the Research Ethics Committee of Augusto Motta University Centre (CAAE: 46245215.9.0000.5235). All patients who met the eligibility criteria signed an informed consent form prior to the study procedure. As the Standards for Reporting of Diagnostic Accuracy Study for Artificial Intelligence (STARD-AI) is currently in development (Sounderajah et al., 2021), we have adhered to the STARD guidelines to the extent possible while reporting this study (Bossuyt et al., 2015).

2.2. Data source

We included patients (aged ≥18 years) with musculoskeletal pain from two outpatient physical therapy private clinics (Gaffrée and Guinle University Hospital and Augusto Motta University Center) and an outpatient multidisciplinary rehabilitation service (Cabo Frio Rehabilitation Center) in Rio de Janeiro, Brazil. We defined musculoskeletal pain as pain from muscle, ligament, bone, or joint origins (Murray et al., 2013). Patients with acute or chronic pain (i.e., pain lasting more than three months) were eligible for inclusion in the study. However, patients with a history of spinal surgery, rheumatologic diagnosis, tumors, pregnancy, illiteracy, or inability to complete self-reported questionnaires were excluded.

2.3. Features (Sociodemographic, lifestyle and clinical variables)

Before the CPM protocol, we collected sociodemographic data (age, sex, weight, height, body mass index, and educational level) as well as lifestyle information (physical activity, sleep). Clinical features included pain, fatigue, central sensitization, psychological disorders, neuropathic-like symptoms, and disability level. We collect clinical data using Numeric Pain Rating Scale (NPRS), Central Sensitization Inventory (CSI) (Mayer et al., 2012; Neblett et al., 2013, 2017), Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) (Wolfe et al., 2016); PainDETECT (PDQ) (Freynhagen et al., 2016); and Patient-Specific Functional Scale (PSFS) (Kowalchuk Horn et al., 2012) (see Supplementary material for details).

2.4. Outcome (Endogenous inhibitory pain response)

Test Stimulus (Pressure Pain Threshold - PPT): A digital pressure algometer (model Force Ten FDX, Wagner Instruments, Greenwich, USA) was used before and after 1 min of the cold pressor test. The distal part of the dorsal forearm and tibialis anterior muscle of the dominant members were evaluated. The two sites were evaluated in the same order for all participants. Patients were familiarized with the pressure algometer by applying pressure to the dominant forearm to ensure that the test had been understood. and pressure was gradually increased (1 kgf/s) until the patient gave the verbal command "pain". The force was gradually increased (1 kg-force/s) until the feeling of pressure from the primary subject changed to pain. The pressure pain threshold was recorded in kilograms-force (kgf) when the patient gave the verbal command "pain".

Conditioning stimulus (Cold-Pressor Task - CPT): Participants were asked to submerge their non-dominant hand in a bucket of cold water (1–4 °C) with temperature-controlled by a thermometer (5130 model, Incoterm) for up to 1 min. They were instructed to keep their hand in the water without moving or making muscle contractions. Participants could withdraw their hand when they could no longer tolerate the pain stimulus. The room environment, including temperature, humidity, lighting, and noise, was controlled during the procedure.

Assessment of inhibitory pain response: To evaluate the endogenous inhibitory pain response (CPM efficacy), the CPT was immediately followed by a second PPT. The classification of CPM efficacy was based on evidence of impaired pain modulation at two sites. Only patients with CPM inefficacy in both locations (the anterior tibialis muscle and distal part of the dorsal forearm) were classified as having impaired pain modulation. Upper and lower limb sites were used to avoid the inclusion of patients with peripheral sensitization according to the recommendations for conditioned pain modulation (Yarnitsky et al., 2015). The efficacy of CPM was assessed by calculating the difference between the PPT values (delta PPT, differences between final and initial values). Negative values represent an inefficacy of the CPM, and null or positive values were considered as a typical response of the CPM (Yarnitsky et al., 2015).

2.5. Data preparation

Prior to develop the machine learning models, we conducted data preprocessing to detect and handle missing and noisy values, and to transform variables where necessary (Kuhn and Johnson, 2013). Although there are several methods to deal with missing data, we applied list-wise deletion, which involves removing cases that have any

missing values from the dataset (Emmanuel et al., 2021). We conducted a visual inspection of the correlation matrix and the variance inflation factor (VIF) to identify non-collinear features. If the VIF value exceeded 10, we excluded the variable due to multicollinearity. To address class imbalance, we employed the Synthetic Minority Over-Sampling Technique (SMOTE), which involves generating synthetic examples along the line segments connecting the *k* nearest minority class neighbors to oversample the minority class (target variable) (Chawla et al., 2002). StandardScaler was applied in numeric features prior to training logistic regression, and support vector machine (SVM). Sample size calculation was performed for the original study (Bezerra et al., 2021).

2.6. Machine learning models

Our data analysis and machine learning model development were conducted using Python (version 3.9.5) and the following libraires: NumPy (version 1.20.3) for numerical computations, Pandas (version 1.2.4) for data manipulation and analysis, Statsmodels (version 0.12.2) for data handling, Seaborn (version 0.11.1) for data visualization, and Scikit-learn (version 0.24.2) for training and testing machine learning algorithms, SHapley Additive exPlanations (SHAP, version 0.41.0) and Local Interpretable Model-agnostic Explanations (LIME, version 0.2.0.1). We developed and explored five supervised machine learning algorithms for predicting CPM efficacy: decision tree, random forest (an ensemble of multiple decision trees with bootstrap aggregation), eXtreme Gradient Boost (XGBoost), logistic regression, and SVM. The dataset was split into 70% for training and 30% for testing. To evaluate the predictive ability of our model on new data, we conducted the training process using 10-fold cross-validation. Cross-validation is a technique that involves splitting the data into multiple subsets or "folds", training the model on some of the folds, and then testing its performance on the remaining fold(s). We chose this method to prevent overfitting, which occurs when the model fits exceptionally well for the training data but fails to perform well on new data, or underfitting, which results when the model cannot adjust to the inherent variability of the data. By using cross-validation, we were able to test the model's ability to predict outcomes for new data that were not included in the initial estimation process (Hastie et al., 2009; Berrar, 2019).

2.7. Model tunning

Several automatic hyperparameter optimization methods have been developed (Bischl et al., 2023). We used the Grid Search approach to optimize the performance of each model by identifying the optimal hyperparameters. Grid Search is a technique that involves providing a set of hyperparameters and their corresponding values to an algorithm, which then performs an exhaustive search over all possible combinations of the given values. The model was trained for each set of hyperparameters, and the Grid Search algorithm compared the performance score of each trained model to determine the best one. We used 10-fold cross-validation (i.e., training the model on 10 different folds using different hyperparameter combinations) (Appendix A) (Agrawal, 2021).

2.8. Model performance assessment

Accuracy, sensitivity, specificity, positive and negative predictive values, precision, recall, F1-score, area under the receiver operating characteristic curve (AUROC), Matthews' Correlation Coefficient (MCC) and Cohen's kappa were used to explore the performance of each model (Bradley, 1997; Erickson and Kitamura, 2021). The Matthews Correlation Coefficient (MCC) is a metric that considers true positive, false positive, true negative, and false negative predictions to produce a score between −1 and 1. A score of 1 indicates perfect predictions, 0 indicates random predictions, and −1 indicates complete disagreement between the predictions and true labels. MCC has been reported to be a reliable metric for classification tasks (Chicco et al., 2021). Cohen's kappa coefficient was used to evaluate the agreement between predicted and observed values (Vieira et al., 2010).

2.9. Interpretability and post-hoc explanation

To quantify the impact of each feature on prediction scores (feature relevance), we applied the SHapley Additive exPlanations values (SHAP) Python package. This package utilizes a game-theoretic approach to evaluate the importance of each feature in a model. The Shapley value is defined as the average marginal contribution of an instance of a feature among all possible combinations of features (Lundberg et al., 2020; Štrumbelj and Kononenko, 2014). The mean SHAP values of the model with best performance were calculated after conducting 10 iterations. In addition to SHAP, we used the Local Interpretable Model-Agnostic Explanations (LIME). LIME is a model-agnostic technique that can explain the predictions of any black-box machine learning model, providing insights into the model's decision-making process at the individual prediction level, rather than offering only a global explanation of how the model works (Belle and Papantonis, 2021). In this study, we applied the LIME framework to generate explanations for the CPM efficacy in a single patient under two different scenarios (preserved and impaired CPM).

3. Results

3.1. Characteristics of dataset

The dataset comprised 311 patients with musculoskeletal pain and 31 variables. A total of 61 (24.4%) patients were classified as having inefficacy of CPM. We excluded 64 (21%) patients due to missing data and 20 variables due to multicollinearity. Appendix B presents the VIF measurements for each feature included in the machine learning models. The resulting dataset used for training and testing our algorithms consisted of 247 patients (199 with preserved CPM and 48 with impaired CPM efficacy) and 11 variables (10 features and 1 target) (Fig. 1) The oversampling technique resulted in a balanced dataset of 141 patients with preserved CPM and 141 with impaired CPM efficacy. The sample characteristics are presented in Table 1.

3.2. Model performance

Table 2 presents the performance results for each algorithm. The XGBoost model presented the highest performance among the five models evaluated in this study, with an accuracy of 0.81 (95% CI = 0.73 to 0.89), F1 score of 0.80 (95% CI = 0.74 to 0.87), AUC of 0.81 (95% CI: 0.74 to 0.88), MCC of 0.61, and Kappa of 0.61. The MCC and Kappa values for the XGBoost model were also higher than those of the other models, suggesting better agreement between predicted and observed outcomes. These results indicate that the XGBoost model is better at predicting the CPM efficacy in this dataset.

3.3. Interpretability and post-hoc explanation

Fig. 2 presents the results of applying SHAP (Fig. 2A and B) and LIME (Fig. 2C and D) algorithms to the XGBoost model. The SHAP plot displays the features ordered by their importance, with the most significant feature located at the top. In Fig. 2A, the mean absolute SHAP values are depicted to illustrate the mean impact of each feature on the model's output. In Fig. 2B, the local explanation summary provides insight into the relationship between each variable and CPM classification, illustrating the direction of the relationship between each variable and CPM classification. Each point in the beeswarm plot represents a SHAP value for a specific observation. The points are colored according to the value of the corresponding feature, with red indicating high values and blue indicating low values. This plot provides insight into how the value of each feature affects the model's output for individual observations. The

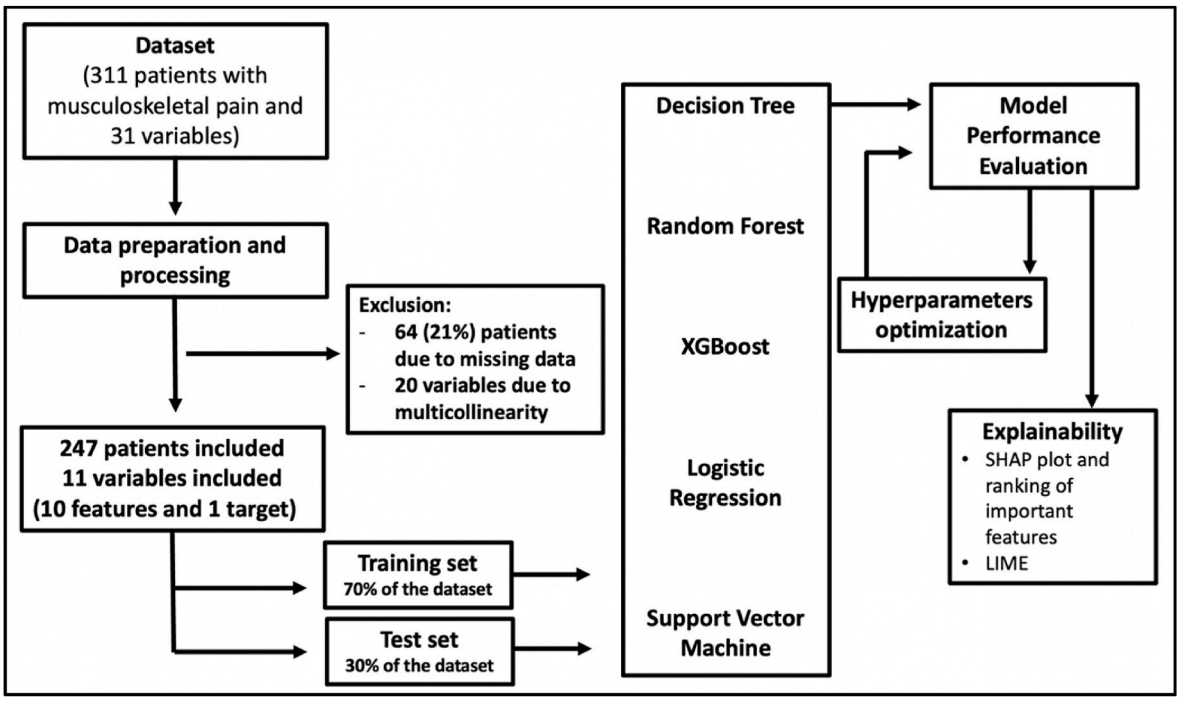

Fig. 1. Overview of the study flow.

XGBoost model was found to be predominantly influenced by pain duration, fatigue, physical activity, and the number of painful areas, with these features having the highest impact on the model's predictions. Conversely, symptoms of central sensitization, anxiety, and depression had lower levels of influence on the model's output.

Based on LIME results shown in Fig. 2C, the XGBoost model predicts impaired CPM efficacy for a specific patient with 94% confidence. This prediction is primarily influenced by the patient's low level of physical activity, the duration of pain being more than seven months, and the presence of pain in more than eight body regions. On the other hand, in Fig. 2D, the model predicts preserved CPM efficacy with 71% confidence for a patient who is physically active, experiences no sleep problems, and being male.

4. Discussion

4.1. Main results

In this study, we aimed to explore the performance of five machine learning models in predicting the efficacy of the endogenous pain inhibitory pathway. In addition, we employed SHAP and LIME to identify the contribution of individual features to our models' predictive performance. By utilizing these approaches, we were able to rank the features that exerted the most significant influence on the model's output, providing insight into the underlying factors driving the predictions.

The XGBoost model demonstrated superior performance on our dataset, which can be attributed to its use of gradient boosting on decision trees. This approach involves creating a sequence of models that iteratively correct the errors of the previous models, resulting in an optimal final model (Chen and Guestrin, 2016). The model was influenced by duration of pain, fatigue, physical activity, and the number of painful areas, with these features having the highest impact on the model's predictions. Symptoms of central sensitization, anxiety, and depression had lower influence on the model's output. By applying LIME to illustrate two individual cases, we obtained their respective CPM classification predictions, along with the corresponding feature importance values. This approach enabled us to gain insights into how each feature influences the model's predictions for these specific patients. Such local interpretation can be particularly valuable in clinical practice.

4.2. Comparison with literature

Several factors such as age, sex, menstrual phase, attention, expectations, physical activity, race, genetics, and psychological factors (anxiety, depression, and catastrophizing) seem to influence the CPM efficiency. However, these findings come from different settings, protocols and populations (Ramaswamy and Wodehouse, 2021; Clark et al., 2017). The duration of pain (in months) had the most significant impact on the model's predictions. A systematic review of 30 studies was conducted to investigate whether CPM is impaired in individuals with chronic pain conditions. The findings revealed that almost 70% of the comparisons indicated a statistically significant decrease in CPM among chronic pain patients, with a large effect size ($d = 0.78$) (Lewis et al., 2012b). On the other hand, the categorical variable (acute or chronic pain) ranked sixth in terms of influence duration of pain. Thus, it is possible that pain duration as a numerical variable may exert greater influence in future models. Fatigue was the second feature in terms of influence on the model. However, the relation between fatigue levels and CPM efficacy have been less explored in the literature. Jarrett et al. (2014), with a small sample of women with irritable bowel syndrome, found that patients with low CPM efficiency also reported more days with moderate to severe fatigue. Physical activity classification was the third feature in terms of influence on the model. In fact, pain modulation seems to be more efficient in individuals who report high level of physical activity (Mertens et al., 2021; Umeda et al., 2016; Shiro et al., 2017; Fiedler et al., 2021). Regarding number of painful areas, Gerhardt et al. (2017), reported that patients with local chronic low back pain showed significantly higher CPM compared with patients with chronic widespread back pain. An association of larger body pain distribution with lower CPM was reported for patients with chronic widespread back pain (Gerhardt et al., 2017) and central neuropathic pain (Gruener et al., 2016).

Table 1
Sociodemographic and clinical characteristics of participants.

Variables	n = 247
Age (years), mean (Sd.)	52 (14.7)
Sex, n (%)	
Women	170 (69%)
Men	77 (31%)
Practice of physical activities, n (%)	
Yes	132 (53%)
No	115 (47%)
Pain duration (>3 months), n (%)	
Yes	220 (89%)
No	27 (11%)
Pain Duration (months), mean (Sd.)	64.5 (97.9)
Functional limitation (0–10), mean (Sd.)	7.1 (2.0)
Number of Painful areas, mean (Sd.)	6.1 (6.0)
Symptom Severity Scale (0–12), mean (Sd.)	5.4 (2.7)
Fatigue perception in the last week, n (%)	
No problem	50 (20%)
Slight or mild problem	55 (22%)
Moderate problem	88 (36%)
Severe problem	54 (22%)
Sleep quality in the last week (Waking unrefreshed), n (%)	
No problem	70 (28%)
Slight or mild problem	54 (22%)
Moderate problem	57 (23%)
Severe problem	66 (27%)
Clinical diagnosis of anxiety, n (%)	
Yes	64 (34%)
No	183 (66%)
Clinical diagnosis of depression, n (%)	
Yes	58 (23%)
No	189 (77%)
Central Sensitization Inventory(CSI) (0–100), mean (SD)	34.2 (17)
Symptoms of Central Sensitization, n (%)	
Yes	164 (66%)
No	83 (34%)
Score painDETECT questionnaire (PDQ) (>19), n (%)	
Yes	51 (21%)
No	196 (79%)
Pain (0–10), mean (SD)	
Pain intensity at the moment	5.9 (2.4)
Higher pain intensity (last 4 weeks)	8.1 (2.0)
Mean pain intensity (last 4 weeks)	6.6 (2.1)
Efficacy of Conditioned Pain Modulation	
Impaired	48 (17%)
Preserved	199 (83%)

Note: Continuous variables are expressed in mean (Sd. – standard deviation) and categorical variables in frequencies.

4.3. Strengths and limitations

Machine learning techniques have been used in pain research with different aims. These include classification and diagnosis of patients with chronic pain using structured health data, classification and diagnosis of patients with chronic pain using text and images, genomics approaches and pain biomarker identification, pain treatment, self-management, and measurement of pain intensity via facial expression (Jenssen et al., 2021). However, to the best of our knowledge, this is the first study to explore ML algorithms in mapping features to established CPM efficacy classes. The current approach aimed to address the challenge of inconsistent findings in previous literature on the factors that influence the CPM efficacy (Ramaswamy and Wodehouse, 2021; Clark, 2017) by using a standardized approach, controlling for time of immersion, water temperature, and using the same test stimulus in a sample of patients with chronic musculoskeletal pain.

The current study has several limitations. First, the sample size can be considered small with only 247 participants and 48 patients with impaired CPM. Although we applied an oversampling technique to balance our dataset, the prediction performance of the ML model may be affected. Other techniques such as using a combination of multiple sampling methods or collecting new data may be required. Second, we

Table 2
Evaluation results of predictive models using five artificial intelligence algorithms.

Model	Accuracy Mean (95%CI)	Sensitivity Mean (95%CI)	Specificity Mean (95%CI)	PPV Mean (95%CI)	NPV Mean (95%CI)	AUC Mean (95%CI)	Precision Mean (95%CI)	Recall Mean (95%CI)	F1-score Mean (95%CI)	Cohen's kappa Mean	MCC Mean
SVM	0.75 (0.69–0.80)	0.71 (0.64–0.78)	0.79 (0.71–0.86)	0.82 (0.73–0.90)	0.72 (0.62–0.77)	0.74 (0.69–0.80)	0.82 (0.73–0.90)	0.67 (0.59–0.76)	0.72 (0.66–0.78)	0.49	0.47
Logistic Regression	0.67 (0.61–0.73)	0.66 (0.59–0.74)	0.68 (0.61–0.76)	0.70 (0.64–0.76)	0.68 (0.62–0.74)	0.67 (0.62–0.73)	0.70 (0.64–0.76)	0.64 (0.55–0.74)	0.66 (0.60–0.72)	0.35	0.31
Decision Tree	0.78 (0.73–0.83)	0.77 (0.70–0.83)	0.80 (0.73–0.87)	0.82 (0.76–0.88)	0.79 (0.72–0.86)	0.78 (0.74–0.82)	0.82 (0.76–0.88)	0.75 (0.64–0.86)	0.77 (0.71–0.82)	0.56	0.43
Random Forest	0.79 (0.71–0.87)	0.75 (0.69–0.82)	0.83 (0.76–0.90)	0.77 (0.69–0.84)	0.76 (0.70–0.83)	0.79 (0.72–0.86)	0.85 (0.77–0.94)	0.72 (0.62–0.82)	0.77 (0.69–0.84)	0.57	0.48
XGBoost	0.81 (0.73–0.89)	0.79 (0.73–0.86)	0.82 (0.75–0.88)	0.86 (0.76–0.95)	0.80 (0.75–0.86)	0.81 (0.74–0.88)	0.86 (0.76–0.95)	0.79 (0.70–0.88)	0.80 (0.75–0.76)	0.61	0.61

Abbreviation: SVM: Support Vector Machine; PPV, Positive Predictive Value; NPV, Negative Predictive Value; MCC: Matthews Correlation Coefficient.

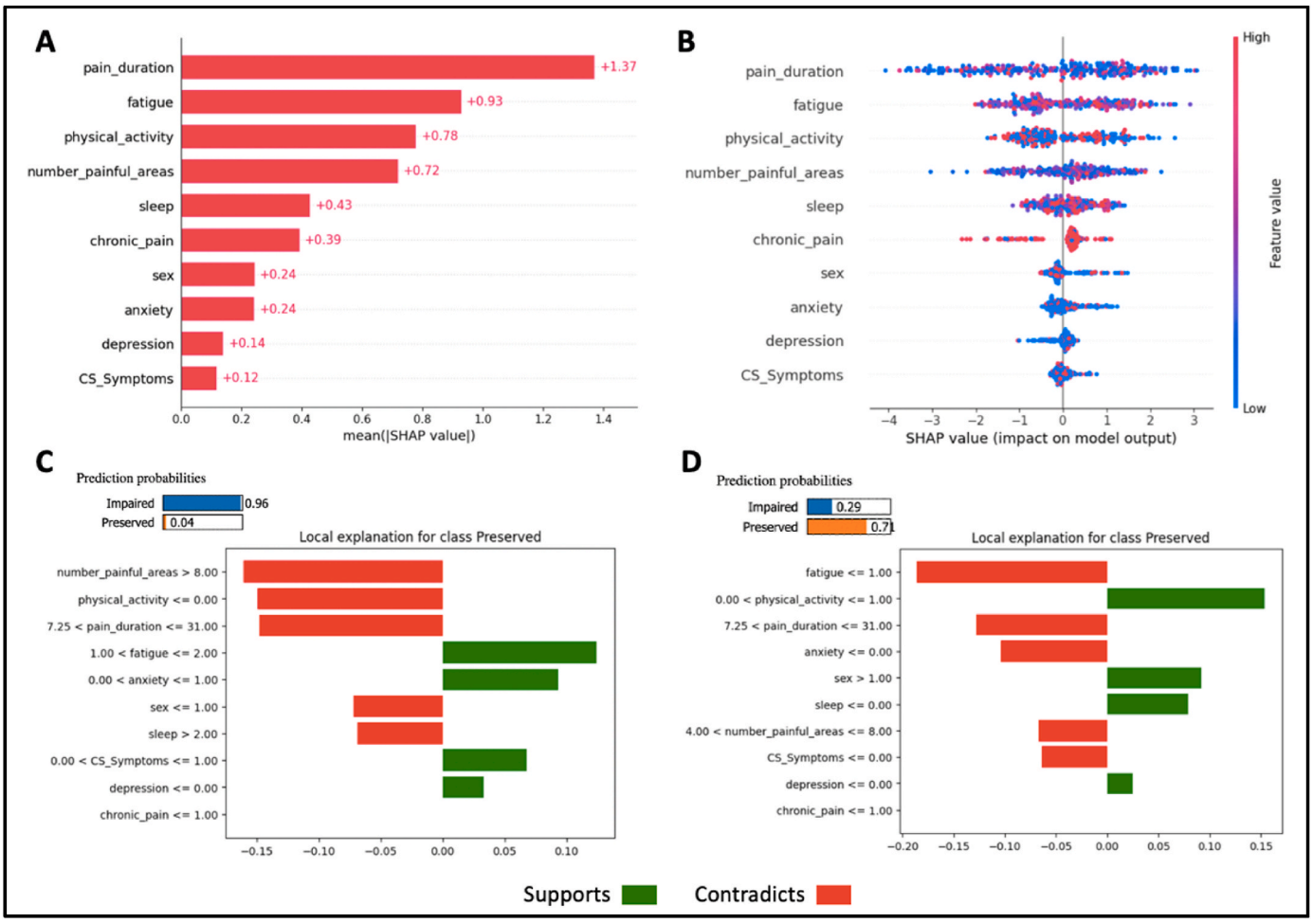

Fig. 2. The model's interpretation. Fig. 2A and B. The XGBoost model explanation based on the SHAP algorithm. (A): The importance ranking of the variables according to the mean (|SHAP value|); (B): Beeswarm plot showing the attributes of the features in the model. Each line represents a feature, and the abscissa is the SHAP value, which represents the degree of influence on the predicted outcome. Each dot represents a sample. The redder the color, the greater the value of the feature, and the bluer the color, the lower the value. Fig. 2C and D. Local interpretable model-agnostic explanations (LIME) modeling results individualized per patient. Feature values (y-axis), and feature weight's effect as they support or contradict Conditioned Pain Modulation (CPM) efficacy (x-axis). In Fig. 2C, the patient is shown to have a 96% probability of impaired CPM due to having more than eight painful body areas, being physically inactive, having a pain duration of more than seven months, being female and moderate or severe sleep problems. In Fig. 2D, the patient is shown to have a 71% probability of preserved CPM, attributed to being physically active, male, having no sleep problems, and no history of depression. Abbreviation: CS – Central Sensitization. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

applied list-wise deletion which can be considered the simplest approach. We recognize that this approach may also result in in biasness and other strategy should be tested to improve models' performance (Emmanuel et al., 2021). Third, it is worth mentioning that other protocols to measure CPM efficacy may yield different results. Fourth, although explanation provided by LIME is clinically relevant (Kumarakulasinghe et al., 2020), LIME explanations are only local and may not generalize to other features or populations (Belle and Papantonis, 2021). Finally, it is worth noting that the models developed in this study exhibit a high level of complexity, primarily due to the inclusion of a large number of features. It should be noted that these models be appropriate for the dataset employed in this study. Therefore, the external validity of this model should be tested in future studies before clinical implementation.

4.4. Implications for clinical practice and future research

The exploratory analysis of each prediction model developed in the current study can contribute to the present knowledge on descending pain modulatory pathways and can be useful in clinical practice and further research. First, the prediction model consisted of personal and clinical features that are commonly measured in patient encounter forms. Second, this model may contribute to the development of a standardized and accurate protocol for predicting the CPM efficacy in future studies. Third, the development of an alternative approach to predict the CPM efficacy without exposing patients to a painful stimulus and/or when a painful stimulus is unavailable is a significant step forward in pain research. It eliminates the need for painful procedures, reduces the patient's discomfort, and makes the prediction of CPM efficacy using clinical questions or questionnaires.

5. Conclusion

We found that XGBoost model demonstrated superior performance on our dataset. The SHAP method was used to identify the most influential features in the models, highlighting the importance of duration of pain, fatigue, physical activity, and the number of painful areas, with these features having the highest impact on the model's predictions of CPM efficacy. These findings can contribute to the development of more accurate and effective models for predicting pain modulation. However, further research is needed to test the model's external validity and its clinical utility.

Ethical approval

CAAE: 46245215.9.0000.5235.

Declaration of generative AI and AI-assisted technologies in the writing process

None.

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.msksp.2023.102788.

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EDITORIAL

Pain in COVID-19 patients: A call to action for physical therapists to provide pain management after an episode of COVID-19

The coronavirus disease 2019 (covid-19) is an ongoing public health problem worldwide. Covid-19 is an infectious condition caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and was recognized as a global pandemic in March 2020,[1] causing two million deaths by March of 2021, according to the World Health Organization.[1] In Brazil, the number of confirmed cases and deaths by Covid-19 in March 2021 was more than 12.9 million and 328,000, respectively.[1]

Covid-19 is now identified as a multi-organ disease with a broad spectrum of clinical manifestations. Although covid-19 most frequently affects the respiratory and cardiovascular system, the musculoskeletal system, central nervous system, and peripheral nervous system are also affected.[2] The most commonly reported symptoms among patient post-acute covid-19 include fatigue, dyspnea, muscular weakness, anxiety, depression, cognitive disturbance, headaches, hair loss, and chest pain.[3] Pain can be a frequent complaint in patients after covid-19,[4] but it remains overlooked and not well understood. Some patients with chronic pain may experience worsening symptoms resulting from covid-19 due to personal issues or decreased healthcare provision.[5] In this context, we highlight the possibility of some patients developing pain symptoms as a consequence of covid-19 resulting as part of a post-viral syndrome or deterioration due to exacerbation of preexisting physical symptoms, mental complaints, or lifestyle factors (e.g., insomnia, physical inactivity).

Clinicians should be mindful that patients with post-acute covid-19 may report several musculoskeletal and neurological manifestations. The most common musculoskeletal symptoms include myalgia (19%), headache (12%), back pain (10%), muscle weakness (1.6%), skeletal muscle injury (1.6%), arthralgia (1.6%), and facial muscle pain (1.6%).[2] Brazilian patients with covid-19 presented myalgia, fatigue, and headache as initial symptoms.[6] Nonetheless, it is now well established that covid-19 presents peripheral or central neurological complications.[7] Dizziness (10%), smell impairment (35%), taste impairment (33%), acute cerebrovascular disease (3%), ataxia (3%), impaired consciousness (2%), and impaired vision (1.6%) are examples of neurological manifestations reported by patients with covid-19.[2] Neuralgia, hyperalgesia, and allodynia are other neurological symptoms present in patients with covid-19.[8]

Clinicians should also recognize the relevance of identifying pain phenotypes correctly. For instance, it has been suggested that infections may directly impact the peripheral nervous system or central nervous system or induce post-viral immune syndrome favoring the development of neuropathic pain.[4] Frequently, patients with neuropathic components present unfavorable outcomes compared to patients with nociceptive pain. Methods to discriminate between mechanism-based categories of musculoskeletal pain have been presented in a recent systematic review.[9] Therefore, assessing the pain phenotypes in patients with persistent covid-19 symptoms provides important insights to physical therapists.

Given the global SARS-CoV-2 pandemic, we draw clinicians' attention to recognize post-acute covid-19 as a multi-organ disease.[10] Research priorities in the physical therapy field should include clinical studies to develop an evidence-based approach for caring for these patients considering persistent symptoms after recovery from acute covid-19 as a current public health problem. Additionally, the potential of tailored treatment for patients with persistent symptoms who were discharged or not admitted to hospitals must be investigated in future studies. Considering the large number of patients with covid-19 in Brazil, rehabilitation services should be prepared to offer adequate pain treatments aiming to reduce the impact that this disease can have on individuals and society now and in the future.

Declaration of competing interest

The authors declare no conflicts of interest.

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Capítulo 3 Manuscrito para Submissão

NOTA SOBRE MANUSCRITOS PARA SUBMISSÃO

Este arquivo contém manuscrito(s) a ser(em) submetido(s) para publicação para revisão por pares interna. O conteúdo possui uma formatação preliminar considerando as instruções para os autores do periódico-alvo. A divulgação do(s) manuscrito(s) neste documento antes da revisão por pares permite a leitura e discussão sobre as descobertas imediatamente. Entretanto, o(s) manuscrito(s) deste documento não foram finalizados pelos autores; podem conter erros; relatar informações que ainda não foram aceitas ou endossadas de qualquer forma pela comunidade científica; e figuras e tabelas poderão ser revisadas antes da publicação do manuscrito em sua forma final. Qualquer menção ao conteúdo deste(s) manuscrito(s) deve considerar essas informações ao discutir os achados deste trabalho.

3.1 Neural mobilisation effects in nerve function and nerve structure of patients with peripheral neuropathic pain: a systematic review with meta-analysis.

3.1.1 Contribuição dos autores do manuscrito para submissão #1

Iniciais dos autores, em ordem:	J.V.B.,	L.A.C.,	M.A.M.P.,	J.P.M.R.,	G.F.T.,	S.M.,	L.A.C.N.,
Concepção	X	X				X	X
Métodos	X	X	X	X	X	X	X
Programação	X	X	X	X	X	X	X
Validação	X	X	X	X	X	X	X
Análise formal	X	X			X	X	X
Investigação	X	X			X	X	X
Recursos	X	X	X	X	X	X	X
Manejo dos dados	X	X	X	X	X	X	X
Redação do rascunho	X	X	X	X	X	X	X
Revisão e edição	X	X	X	X	X	X	X
Visualização	X	X	X	X	X	X	X
Supervisão	X	X				X	X
Administração do projeto	X	X	X	X	X	X	X
Obtenção de financiamento	X	X					X

Contributor Roles Taxonomy **(CRediT)**[3]

[3] Detalhes dos critérios em: https://doi.org/10.1087/20150211

Neural mobilisation effects in nerve function and nerve structure of patients with peripheral neuropathic pain: a systematic review with meta-analysis.

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Abstract

Objective: To assess the effects of neural mobilisation on nerve function and nerve structure of patients with peripheral neuropathic pain.

Methods: For this systematic review with meta-analysis, Medline, Embase, CINAHL, Cochrane Library, and World Health Organization International Clinical Trials Registry Platform were searched without restrictions. Eligibility criteria included randomised and non-randomised studies comparing neural mobilisation versus sham, active or inactive control in adults with peripheral neuropathic pain. Primary outcomes were the change in peripheral nerve cross-sectional area. Secondary outcomes included nerve echogenicity, nerve excursion and nerve conduction. Random effects meta-analysis was conducted. Risk of bias was assessed with the Cochrane Collaboration's tool, and certainty of evidence with the Grading of Recommendations Assessment, Development, and Evaluation framework.

Results: Ten randomised clinical trials and four quasi-experimental studies (total sample = 702 participants) were included. Twelve studies included participants with carpal tunnel syndrome. Two examined the cross-sectional area, revealing improvements in the cross-sectional area after the neural mobilisation. Neural mobilisation improved motor [mean difference = 2.95 (95%CI 1.67 to 4.22) and sensory conduction velocity in short-term [mean difference = 11.74 (95%CI 7.06 to 16.43), compared to control. Neural mobilisation did not alter distal motor or sensory latency.

Conclusion: Neural mobilisation seems to improve the cross-sectional area (very low-quality evidence) and sensory conduction velocity (very low-quality evidence). Neural mobilisation was superior to control in improving motor conduction velocity in patients with peripheral neuropathic pain with moderate quality evidence. Distal motor or sensory latency presented similar results compared to other interventions.

Impact: Neural mobilisation seems to improve the cross-sectional area, albeit with very low-quality evidence, affecting the certainty of these findings. Neural mobilisation improves motor and sensory conduction velocity of patients with peripheral neuropathic pain, but overall evidence is of very low to moderate quality.

Keywords: neural mobilisation; manual therapy; musculoskeletal manipulations; peripheral neuropathic pain; neuralgia; nerve conduction study; systematic review.

Subject: Musculoskeletal, Neuropathic pain.

Issue Section: Review

Introduction

Neuropathic pain is a remarkable cause of suffering and disability. The prevalence of chronic neuropathic pain ranges between 7% and 10% of the general population[1]. A neuropathic component is estimated to be in approximately one-third of the pain syndromes[2]. Neuropathic pain can be classified into central or peripheral. Peripheral neuropathic pain, defined as "pain caused by a lesion or disease of the peripheral somatosensory nervous system"[3], presents with distinct pain characteristics and may require specific treatment. Moreover, neuropathic pain can be associated with musculoskeletal conditions, such as low back pain[4], whiplash disorders[5,6], lateral epicondylalgia[7], and carpal tunnel syndrome[8]. Therefore, the intricate nature of neuropathic pain underscores the need for tailored treatment approaches to address its multifaceted challenges.

Clinical guidelines and consensus statements recommend pharmacologic management as treatment for patients with neuropathic pain[9–12], including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and gabapentin as first-line treatments[9,10,13]. Clinical guidelines also recommend non-pharmacological approaches, such as conservative treatments like exercise and manual therapy[14]. In cases where patients do not respond adequately to previous treatments, invasive procedures may be considered[15]. Given the adverse effects caused by pharmacological interventions, the recommendations available are still inconsistent[16]. Thus, effective and safe approaches are needed for patients with peripheral neuropathic pain.

Neural mobilisation is used to reach the neural structures or surrounding tissue and can be performed manually[17,18]. Neural mobilisation promotes clinical benefits for patients with nerve-related conditions[19–21]. For instance, neural mobilisation benefits back and neck pain patients[19]. Similarly, neural mobilisation presented moderate effects on the flexibility of healthy participants and large effects on pain intensity and disability in low back pain[20]. Moreover, neural mobilisation had moderate to large positive results on pain intensity and disability in musculoskeletal disorders patients[22]. Previous studies have also shown that neural mobilisation reduces intraneural oedema[23] and improves intraneural fluid dispersion[24,25]. There was a simultaneous increase in the magnitude of neural adaptive movement with a straight leg elevation

test and the resolution of the radicular and low back pain symptoms[26]. Although high-quality evidence demonstrates the clinical benefit of the neural mobilisation technique, the effects of the technique on nerve function and structure have not yet been adequately explored and summarised.

Peripheral nerves and their mechanical properties have been studied extensively. Healthy peripheral nerves present a tubular form, alternating hypoechogenic and hyperchogenic zones corresponding to nerve and perineural fibres visible on ultrasonography imaging (USI)[27]. Changes in nerve structure are commonly observed in patients with peripheral neuropathies. For instance, patients with carpal tunnel syndrome showed an increase in the cross-sectional area of the median nerve, increased swelling of the wrist to the forearm, hypoechogenicity, disturbance of the fascicular structure, reduced nerve slipping, and increased vascularity[28]. Similarly, patients with fibular nerve entrapment neuropathy demonstrated an increase in the cross-sectional area of the nerve and an increased fibular to popliteal fossa swelling ratio[28]. Several instruments have been used to assess peripheral nerve structure and function. Nerve conduction tests (i.e., electroneuromyography (ENMG)) and imaging exams (i.e., USI and magnetic resonance imaging (MRI)) are most used. The cross-sectional area and echogenicity of the peripheral nerves can be quantified by USI[28,29]. ENMG could be used in the classification of neuropathies[30] in the assessment of nerve conduction[31], and ENMG findings are correlated with structural abnormalities in the nerve[32]. The USI usually measures the excursion of the peripheral nerves[33,34]. Also, the MRI method has been used in peripheral neuropathies to offer more quantitative features[35]. Therefore, this systematic review aimed to assess the effects of neural mobilisation on nerve function and nerve structure of patients with peripheral neuropathic pain.

Methods

Protocol and Registration

A systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[36]. The protocol was registered in advance with the international Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42022337067).

Data sources and searches

We performed electronic searches of Medline, Embase, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials. We performed the initial electronic search from inception to 1st November 2023 without restrictions on language, publication period, or publication status. Keywords, Medical Subject Headings (MeSH), and other index terms, as well as combinations of these terms and appropriate synonyms across all included databases. See Appendix 1 for the Medline search strategy.

We searched clinical trial databases (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) to identify potentially eligible additional published or unpublished data. We conducted manual search of the reference lists of included studies and previous systematic reviews related to this topic for any further potentially eligible studies.

Eligibility criteria

We included randomised clinical trials and non-randomised intervention studies, which assessed the neurophysiological effects of neural mobilisation in patients with peripheral neuropathic pain. Participants were adults (aged 18 years or over) with one or more clinically diagnosed peripheral neuropathic pain (e.g., carpal tunnel syndrome, sciatica, cubital tunnel syndrome, low back pain with radicular symptoms, cervicobrachial pain). As diagnostic criteria for peripheral neuropathic pain varies in the literature, we considered studies that defined peripheral neuropathic pain via clinical diagnosis, nerve conduction studies, or imaging exams. We included studies that used slider or tensioner techniques. Neurodynamic tests (e.g., straight leg raises, slump test and upper limb neurodynamic tests) are examples of movements used in the sliders and tensioners techniques. We considered studies with neural mobilisation prescribed or performed by a health professional and with any duration of treatment or follow up. Eligible comparator was sham neural mobilisation or active or inactive control.

Some conditions of peripheral neuropathic pain were excluded, such as those related to metabolic disorders (e.g., peripheral diabetic neuropathy), neuropathies associated with viral infections (e.g., post-herpetic neuralgia, HIV, leprosy) and chemotherapy-induced peripheral neuropathies. Moreover, studies were excluded if participants had non-specific or mechanical spinal pain, central spinal canal stenosis, cerebral palsy, paraplegia or quadriplegia, and other major conditions (e.g., fractures,

dislocations). We did not include editorials, comments, letters, correspondence, abstracts, case reports, clinical observations, reviews, or studies with animals

Study selection

Records found through searching were exported to EndNote reference management software (version X9), and two independent review authors (J.V.B. and L.A.C.) screened all search results for potentially eligible studies. Potentially eligible articles based on the title, abstract, and full text were sequentially screened. A third independent review author (L.A.C.N) resolved any disagreement about eligibility.

Data extraction

We extracted data from each included study using a standardised extraction form pre-elaborated. Two independent review authors (J.V.B. and L.A.C.) extracted all data, and a third author (L.A.C.N.) revised the data in case of disagreements. The data extracted included details about the study characteristics (i.e., authors, publication year, and country of origin), study design, participant characteristics (i.e., number of participants and clinical condition), detailed treatment performed, control group information, outcomes, follow-up time points, primary results, and conclusions. We extracted pre-treatment and post-treatment means, standard deviations, and 95% confidence intervals for outcomes of interest. We obtained data from the trial registry where data were not available in the published manuscript. The authors were contacted to avoid missing data.

Outcomes measures

The primary outcome was measures of the nerve structure such as a reduction in the cross-sectional area of the nerve measured by USI, MRI, or other imaging exams.

The secondary outcome measures of the nerve structure were echogenicity (e.g., USI, MRI, or other imaging exams). We were also interested in nerve function by improving nerve excursion (e.g., USI or other imaging exams) and nerve conduction (e.g., ENMG or other nerve conduction tests). We categorised follow-up outcome data of individual studies into short-term outcomes (≤ 3 months), intermediate (between 3 and 12 months), or long-term (≥ 12 months after randomisation).

Data synthesis

We calculated changes from the baseline. We used Cochrane's RevMan calculator to estimate the change from baseline standard deviations, where they were not reported.

The meta-analysis was conducted when an outcome was reported in two or more studies. In cases where meta-analysis was not possible, descriptive analyses were performed. The studies were grouped according to the similarity of the outcomes, and it was not necessary to convert the values to a common metric.

Data analysis

The flow of studies was summarised in a study flow diagram following the PRISMA statement[36]. Study characteristics were reported descriptively. Continuous outcomes are presented as mean differences (MDs) with 95% confidence intervals (CIs) between the intervention and control groups. The meta-analysis was performed using random effects model. The heterogeneity analysis was performed using the I^2 values and considered as moderate I^2 value of 30% to 60%, substantial of 50% and 90%, and considerable heterogeneity in values more than 75%, following The Cochrane Handbook of Systematic Reviews of Interventions recommendations[37].

Risk of bias and certainty of evidence

We assessed the risk of bias using the original Cochrane Risk of Bias (ROB) tool for randomised trials[38] and the Risk of Bias in Non-randomised Studies (ROBINS-I) tool for studies that did not use randomisation to allocate interventions[39]. The classification of the ROB tool includes seven items assessing risk of bias: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of biases. The judgment for each item was classified as low risk, high risk or unclear risk of bias[38]. ROBINS-I tool includes seven items assessing the risk of bias in domains: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to departures from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of reported results. Although an updated version of the Cochrane risk-of-bias tool for randomised trials (RoB 2) is available, we choose to use the ROB

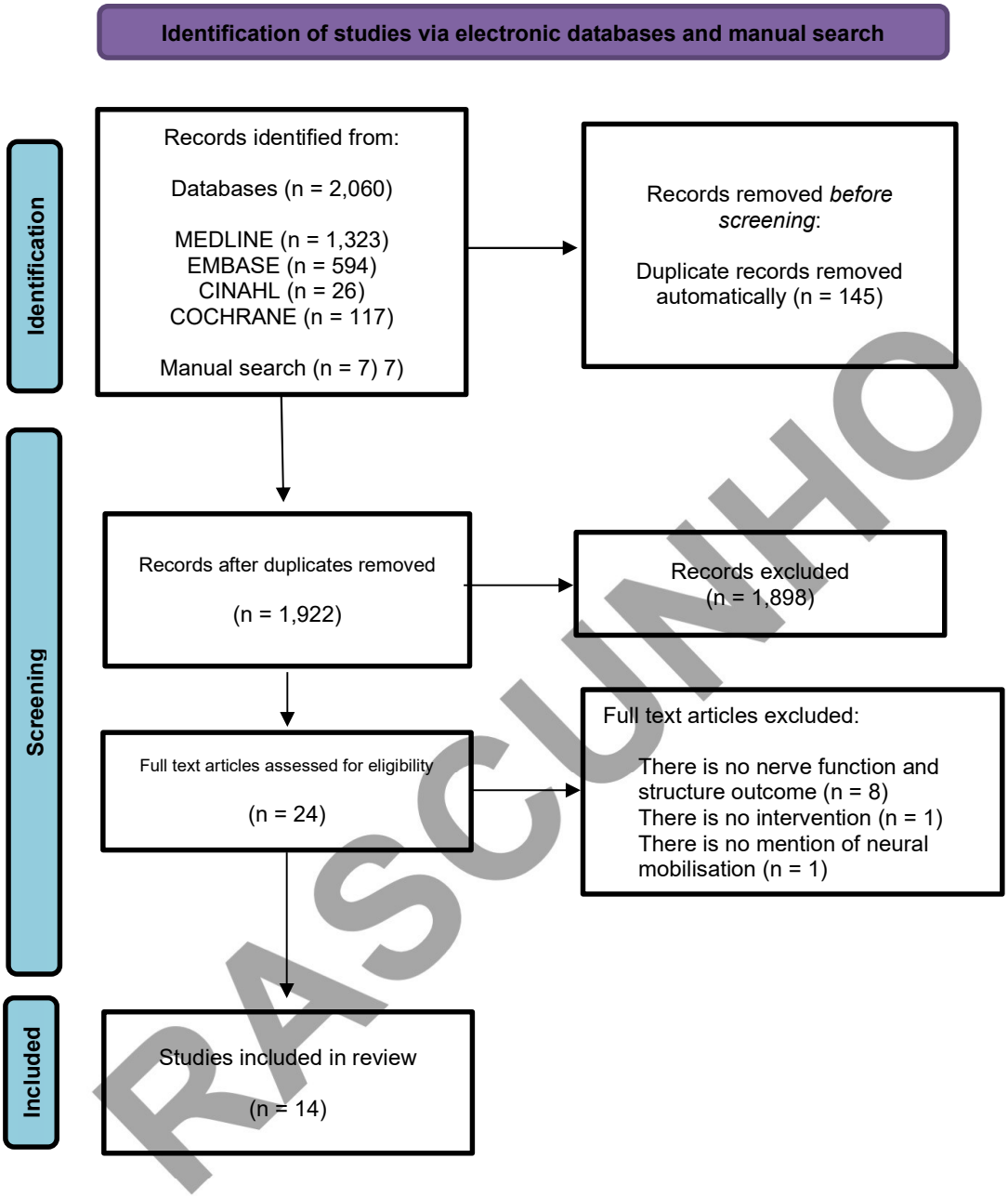
since RoB 2 has low interrater reliability challenges in its application[40]. Two reviewers (J.V.B and L.A.C.) assessed the risk of bias for each study, and a third reviewer (L.A.C.N.) revised in case of disagreements.

The overall quality of evidence was assessed by the Grading of Recommendations Assessment Development and Evaluation (GRADE)[41]. We considered the following items: study design, risk of bias, imprecision, indirectness, inconsistency, and publication bias. The overall quality of evidence per outcome was determined as high, moderate, low, or very low. We present a summary of the overall strength of evidence available using GRADE Summary of Findings table (table 2) produced using GRADEproGTD (https://www.gradepro.org/).

Results

The search retrieved 2,060 records and manual search retrieved 7 records. Of these, we selected 24 for full-text assessment. A total of 14 studies (randomised clinical trials = 10; non-randomised studies of intervention = 4) fulfilled the inclusion criteria (Figure 1).

Figure 1. Flow diagram of search results and studies included.



Characteristics of the studies

Included studies were conducted in 9 different countries, namely Italy[50], Portugal[51], Canada[52], Turkey[8,42,43], United States[45], Australia[23], Sweden[44], Poland[46–48], and Iran[49,53]. The studies included were conducted between 2005 and 2023. Of these, two studies were published in 2009[44,45], two in 2018[43,47], two in 2019[48,51] and two in 2020[49,52]. The characteristics of the included studies are presented in Table 1.

Characteristics of participants

In total, 702 participants of both sexes, aged between 18 and 65 years old, were enrolled in the 14 studies included. Study sample sizes ranged from 14 to 150 participants, with a mean of 52 participants. Twelve studies included participants with carpal tunnel syndrome (randomised clinical trials = 8; quasi-experimental studies = 4). Sciatica and cubital tunnel syndrome were conditions reported by one study each.

Table 1. Descriptions of studies on participants with peripheral neuropathic pain.

Study	Design	Country	Study population	Intervention and comparator	Outcomes measured
Pinar 2005[42]	RCT	Turkey	CTS (n = 26)	Splint plus patient training program *or* splint plus patient training program plus neural mobilisation	Before and 10-week after intervention • NCS (electrophysiologic test): distal motor latency
Baysal et al. 2006[8]	RCT	Turkey	CTS (n = 36)	Splinting plus neural mobilisation or splinting plus ultrasound or splinting plus neural mobilisation plus ultrasound	Before, after intervention, and 8-week after intervention • NCS: motor latency, sensory latency
Bialosky et al. 2009[45]	RCT	United States	CTS (n = 40)	Neural mobilisation or sham technique	Before and after intervention • NCS (electrodiagnostic test): distal motor latency
Svernlov et al. 2009[44]	RCT	Sweden	Cubital Tunnel Syndrome n = 70 (n = 39 women and n = 31 men)	Splinting plus information or neural mobilisation plus information or information	Before and 6-month after intervention • NCS: sensory conduction velocity, motor conduction velocity, electromyography
Schmid et al. 2012[23]	RCT	Australia	CTS (n = 20)	Splinting or neural mobilisation home program	Before, 10-minute after intervention, and 1-week after intervention

					• Nerve structure evaluation: signal intensity
Ginanneschi et al. 2015[50]	QES	Italy	CTS n = 16 [n = 8 hands (men = 1; women = 7) and 8 healthy participants]	Neural mobilisation	Before and after intervention • NCS: sensory conduction velocity, sensory action potential amplitude, distal motor latencies
Wolny et al. 2017[46]	RCT	Poland	CTS (n = 140)	Neural mobilisation plus functional massage plus bone mobilisations techniques or laser plus ultrasound therapy	Before and after intervention • NCS: sensory conduction velocity, motor conduction velocity, motor latency, standardized latency
Yildirim et al. 2018[43]	RCT	Turkey	CTS (n = 21)	Kinesiotaping plus neural mobilisation or neural mobilisation	Before, 3-week after intervention, and 6-week after intervention • Nerve structure evaluation: CSA
Wolny & Linek, 2018[47]	RCT	Poland	CTS (n = 150)	Neural mobilisation or “sham” therapy	Before and after intervention • NCS: sensory conduction velocity, motor conduction velocity, motor latency
Neto et al. 2019[51]	QES	Portugal	Sciatica n = 16	Neural mobilisation	Before and after intervention • Nerve structure evaluation: nerve stiffness (SWV)

			(n = 8 chronic sciatica and n = 8 health participants)		
Wolny & Linek, 2019[48]	RCT	Poland	CTS (n = 103)	Neural mobilisation or control group	NCS: Before and 1-month after treatment • NCS: sensory conduction velocity, motor conduction velocity, motor latency
Paquette et al. 2020[52]	QES	Canada	CTS (n = 14)	Neural mobilisation home program plus videoconference plus logbook	Before and 1-week after the completion of a 4-week intervention program • NCS (US): nerve biological integrity, nerve mechanical properties
Talebi et al. 2020[49]	RCT	Iran	CTS (n = 30)	Nerve mobilisation or mechanical interface mobilisation	Before and immediately after the end of the treatment period • NCS: motor distal latency, sensory distal latency
Khademi et al. 2023[53]	QES	Iran	CTS (n = 20)	Neural mobilisation	Before and immediately after one session of neural mobilisation • Nerve structure evaluation: nerve stiffness • Nerve structure evaluation: CSA

Abbreviations: CSA = Cross-Sectional Area; CTS = Carpal Tunnel Syndrome; NCS = Nerve Conduction Studies; QES = Quasi-Experimental Study; RCT = Randomised Clinical Trials; SWV: Shear Wave Velocity.

Characteristics of interventions

A randomised controlled study compared neural mobilisation versus no treatment in 103 patients with carpal tunnel syndrome[48]. One study compared the effect of neural mobilisation in patients with carpal tunnel syndrome and healthy participants[50]. The other two studies compared the effect of neural mobilisation in a group of patients with carpal tunnel syndrome with no comparison group[52]. One study performed neural mobilisation in patients with sciatica and controls[51]. Four studies compared a group of neural mobilisation versus other interventions[23,42,43,46] or different regimes of neural mobilisation[8,49] for participants with carpal tunnel syndrome. Two studies[45,47] investigated the effects of neural mobilisation compared to the sham technique in participants with carpal tunnel syndrome. One study compared the impact of adding neural mobilisation to information versus other approaches with no neural mobilisation to participants with cubital tunnel syndrome[44].

Seven studies[46–51,53] offered neural mobilisation individually and in person and performed by a physiotherapist. Five studies[8,23,42,44,52] provided a neural mobilisation program that could be carried out at home. The session duration of neural mobilisation ranged from 3 to more than 20 minutes. The frequency of neural mobilisation treatment ranged from only one session to seven sessions per week. Treatment periods varied between one session and 12 weeks.

Outcomes

Cross-sectional area

Two studies examined the cross-sectional area[43,53]. One study found improvements in the median cross-sectional area after neural mobilisation with or without kinesiotaping in patients with carpal tunnel syndrome. Both groups reduced the cross-sectional area short-term, but there was no statistically significant difference in the cross-sectional area between the groups[43]. One study reported a significant cross-sectional decrease in the median nerve immediately after the treatment of neural mobilisation in a non-randomised study[53].

Nerve motor conduction – Distal motor latency

Pooled results showed that neural mobilisation did not improve distal motor latency in the short-term (Mean Difference (MD) [95% CI] = 0.03 metre per second (m/s) [-0.70, 0.75]). However, there was substantial heterogeneity (I^2 = 97%) (Figure 2A). Two hundred and thirty-three participants were involved in the neural mobilisation group, and two hundred and fourteen in the control group.

Five randomised clinical trials tested distal motor latency in the short-term. One study showed that a significant improvement was not found in distal motor latency in groups at short-term[8]. Another study reported a decreased distal motor latency in both groups (i.e., manual therapy with neural mobilisation or electrophysical modalities) in the short-term[46]. Authors showed an improvement of the distal motor latency only for the neural mobilisation group compared to sham[47]. Also, one study reported a lower value of distal motor latency with neural mobilisation compared to the control group in the short-term[48]. Another study showed decreased distal motor latency in both groups (i.e., neural mobilisation or mechanical interface mobilisation) with no difference in the between-group comparison[49]. Overall, these studies were unsuccessful in improving distal motor latency in the short-term.

Nerve motor conduction – Motor conduction velocity

Neural mobilisation improves motor conduction velocity in short-term (MD [95% CI] = 2.95 m/s [1.67, 4.22]) with no heterogeneity (I^2 = 0%) (Figure 2B). Two hundred and six participants were involved in the neural mobilisation group and one hundred eighty-seven in the control group.

Three randomised clinical trials tested motor conduction velocity in the short-term[46–48]. One study showed no significant difference post-treatment between-group comparison (i.e., manual therapy with neural mobilisation or electrophysical modalities) in motor conduction velocity[46]. Other study demonstrated a superior effect on motor conduction velocity of the neural mobilisation compared to sham after the treatment[47]. Moreover, authors reported no significant differences between neural mobilisation and the control groups for motor conduction velocity[48]. Overall, these studies were successful in improving motor conduction velocity in the short-term.

Nerve sensory conduction – Distal sensory latency

Neural mobilisation did not improve distal sensory latency in the immediately after the treatment period (MD [95% CI] = -0.10 m/s [-0.62, 0.41] with low heterogeneity (I^2 = 20%) (Figure 2C). Twenty-seven participants were involved in each group.

Two randomised clinical trials analysed the distal sensory latency immediately after the treatment period[8,49]. One study revealed that the treatment combinations were effective in all groups, but there was no significant difference in the between-group comparison[8]. Moreover, there are significant differences within groups for group 1 (splinting and neural mobilisation) and group 3 (splinting, neural mobilisation, and ultrasound therapy) considering the baseline versus immediately after the treatment period and baseline versus after 8 weeks follow-up[8]. Another study showed no significant improvement in distal sensory latency for the mechanical interface group. In the nerve mobilisation group, there was a significant improvement in distal sensory latency. Moreover, there was no significant difference between the two groups in distal sensory latency immediately after the treatment period ($p > 0.05$)[49]. Overall, these studies were unsuccessful in improving distal sensory latency in the immediately after the treatment period.

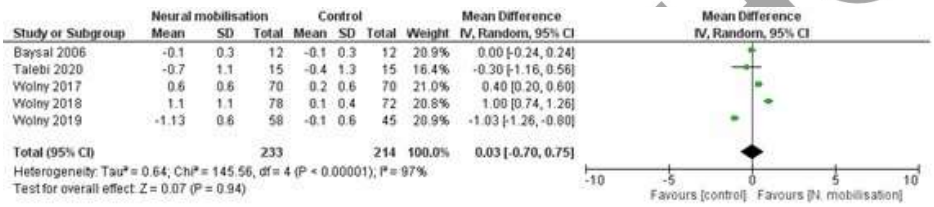
Nerve sensory conduction – Sensory conduction velocity

Neural mobilisation improved sensory conduction velocity in the short-term (MD [95% CI] = 11.74 m/s [7.06, 16.43]) with considerable heterogeneity (I^2 = 77%) (Figure 2D). Two hundred and six participants were involved in the neural mobilisation group, and one hundred and eighty-two in the control group.

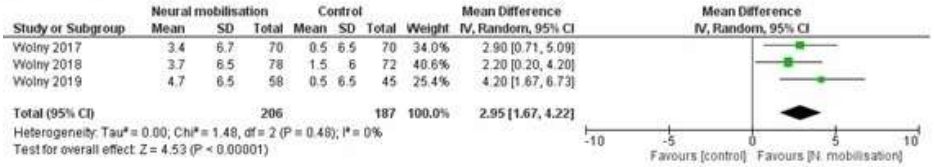
Three randomised clinical trials tested sensory conduction velocity in the short-term[46–48]. One study showed that in the manual therapy group (i.e., neural mobilisation), sensory conduction velocity was increased by 34%. Still, there was no

change in nerve sensory conduction in the electrophysical modalities group [46]. Authors detected a superior effect on sensory conduction velocity of the neural mobilisation than sham after the treatment[47]. Also, other study identified a greater effect favoured neural mobilisation in sensory conduction velocity after ten weeks of treatment (neural mobilisation group: 38.3 m/s, SD = 11.1 vs. control group: 25.9 m/s, SD = 7.72, p < .01)[48]. Overall, these studies were successful in improving sensory conduction velocity in the short-term.

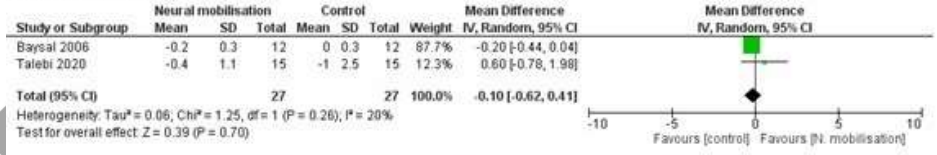
Figure 2. Forest plots: neural mobilisation versus control group.



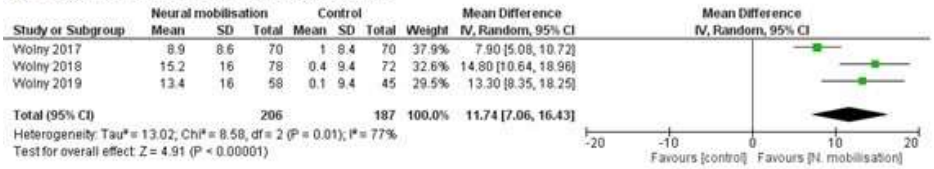
2A. Forest plot of short-term comparison: neural mobilisation versus control group, outcome: distal motor latency.



2B. Forest plot of short-term comparison: neural mobilisation versus control group, outcome: motor conduction velocity.



2C. Forest plot of immediately after the treatment period: neural mobilisation versus control group, outcome: distal sensory latency.



2D. Forest plot of short-term comparison: neural mobilisation versus control group, outcome: sensory conduction velocity.

Descriptive analysis

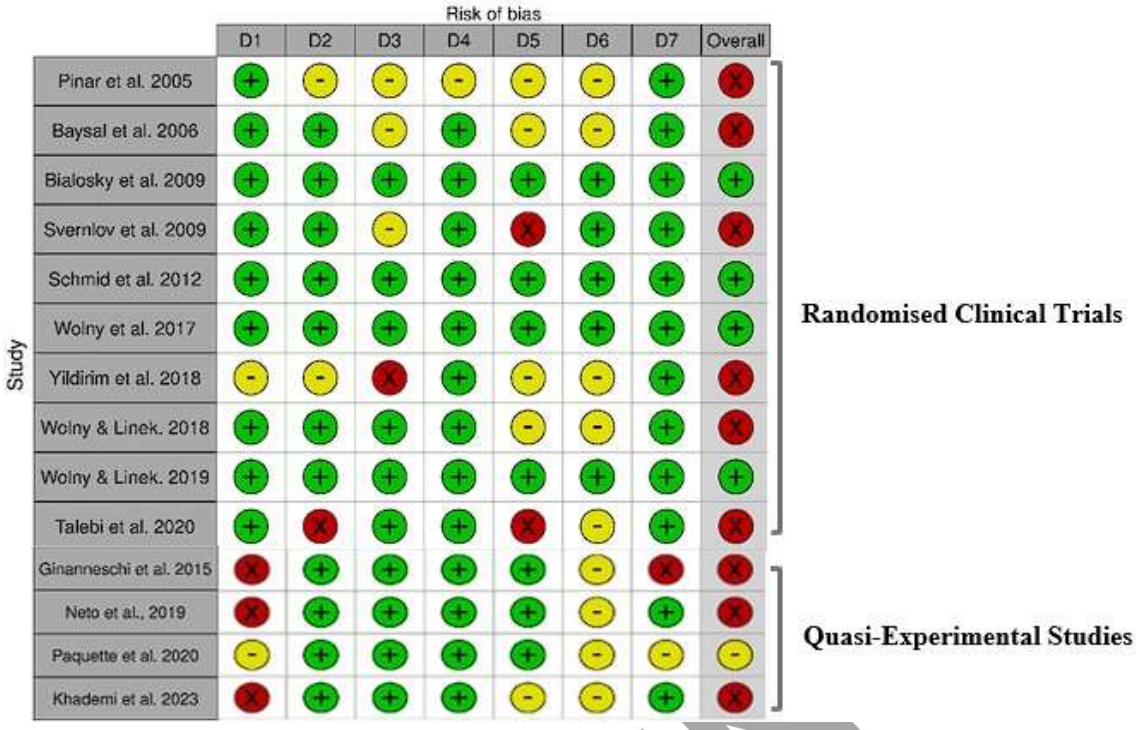
Studies ineligible for pooling

Median nerve cross-sectional area was measured from two studies, but one study did not have control group data[53]. Three outcomes (median nerve signal intensity; sciatic nerve stiffness; and median nerve integrity) were measured from unique studies with no chance of performing a meta-analysis[23,43,51,52]. One study measuring sensory conduction velocity was ineligible for pooling because of the lack of control group data[50].

Risk of Bias and Overall Quality of Evidence

According to the overall evaluation of the risk of bias of the randomised clinical trials included, the risk of bias tool indicated that six articles had a high risk of bias[8,42–44,47,49] and four had a low risk of bias[23,45,46,48] (Figure 3). Most studies scored low risk of bias in domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment and other sources of bias. A high risk of bias was found frequently in incomplete outcome data. Risk of bias of randomised clinical trials and motivation for judgments can be found in Appendix 2. Our results revealed that the three studies presented a low risk of bias in the domains of bias due to the selection of participants, bias in the classification of interventions, bias due to deviations from intended interventions, and bias due to missing data. Moreover, three of the four quasi-experimental studies had a serious risk of bias due to the confounding domain, and in the domain of bias in the measurement of outcomes, all studies present a moderate risk of bias. The overall classification showed that of the four quasi-experimental studies, one had a moderate risk of bias[52], and three had a serious risk of bias[50,51,53] (Figure 3). We considered the certainty of evidence very low for three pooled outcomes (cross-sectional area, distal motor latency, distal sensory latency, and sensory conduction velocity) and moderate for motor conduction velocity (Table 2).

Figure 3. Risk of bias for included randomised clinical trials and quasi-experimental studies.



Note: Risk of bias for included randomised clinical trials domains – D1: random sequence generation; D2: allocation concealment; D3: blinding of participants and personnel; D4: blinding of outcome assessment; D5: incomplete outcome data; D6: selective reporting; D7: other sources of biases; and overall (low, unclear or high risk of bias);

Risk of bias for included quasi-experimental studies domains – D1: bias due to confounding; D2: bias in the selection of participants into the study; D3: bias in classification of interventions; D4: bias due to departures from intended interventions; D5: bias due to missing data; D6: bias in the measurement of outcomes; D7: bias in the selection of reported results; and overall (low, moderate or serious risk of bias).

Table 2. GRADE summary of findings

Neural mobilisation for peripheral neuropathic pain compared to control Population: adults (> 18 years old) with peripheral neuropathic pain Intervention: neural mobilisation Comparison: sham, active or inactive control				
Outcomes	**Mean difference (95% CI) between neural mobilisation and control**	**Number of participants (studies)**	**Confidence in effect estimate**	**Rating**
Cross-sectional area	Not estimated	41 NM + KT = 10 NM = 21 (2)	⊕◯◯◯ Very low	- 1 for risk of bias, - 1 for imprecision - 1 publication bias
Distal motor latency	0.03 (-0.70 to 0.75) p = 0.94)	447 NM = 233; control = 214 (5)	⊕◯◯◯ Very low	- 1 for risk of bias, - 1 for inconsistency, - 1 for imprecision
Motor conduction velocity	2.95 (1.67 to 4.22) p < 0.00001)	393 NM = 206; control = 187 (3)	⊕⊕⊕◯ Moderate	- 1 for imprecision
Distal sensory latency	-0.10 (-0.62 to 0.41) p = 0.70	54 NM = 27; control = 27 (2)	⊕◯◯◯ Very low	- 1 for risk of bias, - 1 for imprecision - 1 publication bias
Sensory conduction velocity	11.74 (7.06 to 16.43) p < 0.00001	393 NM = 206; control = 187 (3)	⊕◯◯◯ Very low	- 1 for risk of bias, - 2 for inconsistency, - 1 for imprecision - 1 publication bias

Note: CI = Confidence Interval; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; KT = kinesiotaping; NM = Neural Mobilisation.

Discussion

This systematic review investigated the effects of neural mobilisation on nerve function and nerve structure of patients with peripheral neuropathic pain. Nerve conduction tests (i.e., electroneuromyography) and imaging exams (i.e., ultrasonography and magnetic resonance imaging) were the most cited instruments used to assess the peripheral nerve's structure and function in peripheral neuropathic pain. Nearly all studies (85%) investigated the effects of neural mobilisation in patients with carpal tunnel syndrome. Four (28%) studies were considered to have a low risk of bias. The median cross-sectional area improvement should be interpreted cautiously since two high-risk-of-bias studies assessed this outcome using neural mobilisation. Neural mobilisation improves motor and sensory conduction velocity in short-term despite the lack of improvement in distal motor latency in short-term and distal sensory latency in immediately after the treatment period. The improvement in the motor conduction velocity was rated with moderate quality of evidence and the other outcomes were rated with very low quality of evidence.

We recognise the strengths and limitations of the present review. To the best of our knowledge, this is the first study that investigated the effect of neural mobilisation on the nerve structure and function of patients with peripheral neuropathic pain. We included only randomised clinical trials and quasi-experimental studies in the systematic review as they provided the best evidence on the effectiveness of neural mobilisation treatment in the nerve function and nerve structure in peripheral neuropathic pain patients. Although our search strategy captured a number of eligible studies, there were limited evidence available on the change of nerve cross sectional area outcome with studies predominately provided data on our secondary outcomes

(nerve conduction tests). The current body of evidence highlights this research area has focussed on a specific group of patients with peripheral neuropathic pain, specifically carpal tunnel syndrome and only study investigated the sciatic nerve. Half (n = 7, 50%) of the studies included were published in the last five years, despite the elevated number of studies (n = 9, 64%) with a high or serious risk of bias.

Neural mobilisation potentially reduces the cross-sectional area of the nerve. Our review found two studies supporting the decrease of the cross-sectional area as a marker of improvement after neural mobilisation in patients with carpal tunnel syndrome[43,53]. Previous studies described a cross-sectional area reduction after surgical procedures for patients with carpal tunnel syndrome[54–56]. Thus, the positive sonography outcome after neural mobilisation is likely due to the favourable clinical findings previously demonstrated in many systematic reviews[19,20,22]. Furthermore, there is a notable relationship between the nerve cross-sectional area and nerve conduction studies in patients with carpal tunnel syndrome[57,58].

Nerve conduction studies are the gold standard for diagnosing peripheral neuropathic pain (e.g., carpal tunnel syndrome), considering the motor and sensory conduction velocity[59]. The current investigation found that neural mobilisation improves motor and sensory conduction velocity in the short-term. We confirmed the positive effect of neural mobilisation on nerve conduction velocity described in two previous systematic reviews that focussed on carpal tunnel syndrome[60,61], using a robust meta-analysis with the change from baseline and expanded the findings to the improvement of the cross-sectional area of the median nerve. Moreover, another systematic review found very low certainty of evidence that neural mobilisation did not affect distal motor latency in patients with carpal tunnel syndrome[62], similar to our findings. Thus, neural mobilisation leads to a partial recovery of nerve function in patients with carpal tunnel

syndrome and possibly in other peripheral neuropathies. The improvement in the nerve conduction velocity may represent a remyelination process after the therapeutic since the conduction velocity evaluates the demyelination of the large-diameter fibres. The current systematic review expands on the effect of neural mobilisation on nerve function and nerve structure for two other clinical conditions. One study described improved nerve conduction velocity of patients with cubital tunnel syndrome who had impairment in the baseline assessment submitted to elbow brace, neural mobilisation, or clinical information interventions [44]. Besides, another study demonstrated an acute decrease in the sciatic nerve stiffness in the symptomatic limb[51].

In clinical practice, the findings from this systematic review suggest that neural mobilisation may be a intervention for patients with peripheral neuropathic pain, particularly those with carpal tunnel syndrome. Improving motor and sensory conduction velocity in the short term indicates a potential benefit in promoting nerve recovery. Clinicians should consider incorporating neural mobilisation into their treatment plans for these patients, keeping in mind the limitations of the current evidence, including the predominance of studies focused on carpal tunnel syndrome and the high risk of bias in many studies. The observed reduction in nerve cross-sectional area after neural mobilisation in carpal tunnel syndrome patients highlights a potential positive impact on nerve structure. However, given the limited research on other peripheral neuropathies and the need for high-quality, well-designed studies to minimise bias, clinicians should approach the integration of neural mobilisation into practice with a balanced consideration of the available evidence and patient-specific factors. The identified biases, such as lack of blinding and incomplete outcome data, underscore the importance of future research efforts' importance in addressing these methodological shortcomings and enhancing the overall quality of evidence in this field.

Few studies have investigated neural mobilisation and its effectiveness in nerve structure and function of patients with peripheral neuropathic pain, considering the same aspects (patient population, technique used, outcome evaluation tool, and follow-up time). Therefore, randomised clinical trials with detailed neural mobilisation schema measured by objective outcomes must facilitate clinicians' decision-making. The most shared bias observed was the lack of blinding of the participant or therapist who administered the therapy, incomplete outcome data and selective reporting. Hence, future high-quality studies should be designed to minimise this bias. Finally, the nerve structure and function parameters are essential in understanding how the nervous system behaviours and their changes can have various implications. These parameters revealed that certain aspects of the nerve's physiology or signal transmission have been altered after the neural mobilisation treatment.

Conclusion

Neural mobilisation seems to improve the cross-sectional area, albeit with very low-quality evidence, affecting the certainty of these findings. Neural mobilisation was superior to control in improving motor conduction velocity in patients with peripheral neuropathic pain with moderate quality evidence. Neural mobilisation was superior in improving sensory conduction velocity and presented similar results in distal motor and distal sensory latency compared to controls in patients with peripheral neuropathic pain based on very low-quality evidence. Our findings should be interpreted cautiously since the majority of the studies included treated patients with carpal tunnel syndrome.

Declarations

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Availability of data and material: Not applicable.

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Appendix 1. Search strategy MEDLINE

Date: 01/11/2023

1- exp Peripheral Nervous System Diseases/
2- Conservative Treatment/
3- Rehabilitation/
4- exp Physical Therapy Modalities/
5- Pain Management/
6- exp Musculoskeletal Manipulations/
7- ((nerve or neural or neurodynamic or nervous) adj3 (mobili#ation or glid* or tension or stretch or slump or physical therapy or physiotherapy or therapy or treatment or modalit*)).mp
8- or/2-7
9- exp Diagnostic Imaging/

10-exp Diagnostic Techniques, Neurological/

11-exp Electrodiagnosis/

12-electroneuromyography.mp

13-nerve conduction tests.mp

14-or/9-13

15-1 and 8 and 14

Appendix 2. Risk of bias of randomised clinical trials studies and motivation for judgments

Risk of Bias		
Title: Can We Use Nerve Gliding Exercises in Women with Carpal Tunnel Syndrome? Reference: Pinar et al. 2005		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were divided into 2 groups through a randomized assignment method."
Allocation concealment (selection bias)	Unclear risk	Not enough information regarding this issue.
Blinding of participants (performance bias)	Unclear risk	Not enough information regarding this issue.
Blinding of outcome assessment (detection bias)	Unclear risk	Not enough information regarding this issue.
Incomplete outcome data (attrition bias)	Unclear risk	
Selective reporting (reporting bias)	Unclear risk	No previous trial registration, but it was clear that the published report included all expected outcomes.
Other sources of biases	Low risk	Not found.
Classification	**High risk**	

Risk of Bias		
Title: Comparison of three conservative treatment protocols in carpal tunnel syndrome Reference: Baysal et al. 2006		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization list was created by a biostatistician."
Allocation concealment (selection bias)	Low risk	"It was given to the physiotherapy department in sealed numbered envelopes." "When the patients qualified to enter the study, appropriate

		numbered envelope was opened at the reception; the card inside indicated the patient's allocation to a treatment group."
Blinding of participants (performance bias)	Unclear risk	No mention of any attempts to blind the participants.
Blinding of outcome assessment (detection bias)	Low risk	"The staff who assessed the outcomes were different from the staff administering the treatments and were blinded to the type of treatment each patient had received."
Incomplete outcome data (attrition bias)	High risk	"The eight dropouts are described as follows: two patients (group II) underwent surgery, two patients (group II) were lost to follow-up. In group III, two patients were lost to follow-up, and another two patients (group III) refused electrophysiologic study due to improvement of symptoms."
Selective reporting (reporting bias)	Unclear risk	No previous trial registration, but it was clear that the published report included all expected outcomes.
Other sources of biases	Low risk	Not found
Classification	**High risk**	

Risk of Bias		
Title: A Randomized Sham-Controlled Trial of a Neurodynamic Technique in the Treatment of Carpal Tunnel Syndrome Reference: Bialosky et al. 2009		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was computer generated, with

		group assignment maintained in sealed, sequentially numbered, opaque envelopes."
Allocation concealment (selection bias)	Low risk	"(…) group assignment maintained in sealed, sequentially numbered, opaque envelopes."
Blinding of participants (performance bias)	Low risk	"(…) group assignment maintained in sealed, sequentially numbered, opaque envelopes."
Blinding of outcome assessment (detection bias)	Low risk	"A licensed physical therapist (J.E.B.) performed all baseline assessments (with the exception of the NCS, which was performed by K.R.V.) and all post randomization assessments until the final session at 3 weeks."
Incomplete outcome data (attrition bias)	Low risk	"The participant not returning for the 3-week follow-up was assigned to the NDT group providing 3-week analysis for 19/20 (95%) participants assigned to receive NDT and 20/20 (100%) participants assigned to receive the sham intervention."
Selective reporting (reporting bias)	Low risk	"The clinical trial registration number is NCT00929123."
Other sources of biases	Low risk	Not found.
Classification	**Low risk**	

Risk of Bias		
Title: Conservative treatment of the cubital tunnel syndrome Reference: Svernlov et al. 2009		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"Informed consent was obtained in all cases and the patients were then randomised using sequentially numbered, sealed envelopes into three groups for different treatments, Group A, Group B and Group C (Fig 1)."
Allocation concealment (selection bias)	Low risk	"All patients were informed about the cause of symptoms and allocated to three groups: night splinting, nerve gliding and control."
Blinding of participants (performance bias)	Unclear risk	No mention of any attempts to blind the participants.
Blinding of outcome assessment (detection bias)	Low risk	"An occupational therapist performed all clinical assessments and instructions. Another, independent, occupational therapist at each centre evaluated the patients before and 6 months after starting the study."
Incomplete outcome data (attrition bias)	High risk	"Six patients, two from each group, completed the conservative treatment program during 3 months."
Selective reporting (reporting bias)	Unclear risk	No previous trial registration, but it was clear that the published report included all expected outcomes.
Other sources of biases	Low risk	Not found.
Classification	**High risk**	

Risk of Bias

Effect of Splinting and Exercise on Intraneural Edema of the Median Nerve in Carpal Tunnel Syndrome—An MRI Study to Reveal Therapeutic Mechanisms Reference: Schmid et al. 2012		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Concealed random allocation was performed by an independent investigator using sealed envelopes."
Allocation concealment (selection bias)	Low risk	"20 patients with mild to moderate CTS were randomly allocated to either night splinting or a home program of nerve and tendon gliding exercises."
Blinding of participants (performance bias)	Low risk	"To verify the inter-tester reliability of the measures, a second investigator blinded to group allocation independently evaluated all MRI scans (JE)."
Blinding of outcome assessment (detection bias)	Low risk	"All MRI scans were coded and an investigator blinded to the group allocation took all measurements (AS)."
Incomplete outcome data (attrition bias)	Low risk	"All participants received the treatment as allocated and adhered to the prescribed exercise program and splinting regime."
Selective reporting (reporting bias)	Unclear risk	No previous trial registration, but it was clear that the published report included all expected outcomes.
Other sources of biases	Low risk	Not found.
Classification	**Low risk**	

Risk of Bias
Title: Efficacy of Manual Therapy Including Neurodynamic Techniques for the Treatment of Carpal Tunnel Syndrome: A Randomized Controlled Trial Reference: Wolny et al. 2017

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned by drawing lots with the group number. Individuals who drew the number 1 were assigned to the MT group, and those who drew number 2 were assigned to the EM group."
Allocation concealment (selection bias)	Low risk	"Participants were randomly allocated to the MT group or the EM group."
Blinding of participants (performance bias)	Low risk	"The procedure in which the patient drew his or her group number was supervised by a secretary who was not otherwise involved in the study."
Blinding of outcome assessment (detection bias)	Low risk	"The specialists who performed the NCS were not aware of the nature of the therapy administered to participants."
Incomplete outcome data (attrition bias)	Low risk	The percentage of withdrawals and dropouts was within the acceptable rate.
Selective reporting (reporting bias)	Low risk	"The clinical trial registration number is ACTRN12614000367640."
Other sources of biases	Low risk	Not found.
Classification	**Low risk**	

Risk of Bias		
Title: Ultrasonographic and clinical evaluation of additional contribution of kinesiotaping to tendon and and nerve gliding exercises in the treatment of carpal tunnel syndrome Reference: Yildirim et al. 2018		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information regarding this issue.

Allocation concealment (selection bias)	Unclear risk	Not enough information regarding this issue.
Blinding of participants (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	Low risk	"The clinical assessment of each patient was performed by a blind investigator (PY) and USG measurements were performed by another blind investigator (BD)."
Incomplete outcome data (attrition bias)	Unclear risk	Not enough information regarding this issue.
Selective reporting (reporting bias)	Unclear risk	Not enough information regarding this issue.
Other sources of biases	Low risk	Not found.
Classification	**High risk**	

Risk of Bias		
Title: Neurodynamic techniques versus "sham" therapy in the treatment of carpal tunnel syndrome; a randomized placebo-controlled trial Reference: Wolny & Linek, 2018		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible patients were randomly allocated to 2 parallel groups: NT or ST using a random number generator."
Allocation concealment (selection bias)	Low risk	"Those who were randomly assigned "1" were in the NT group, and those who were randomly assigned "2" were in the ST group."
Blinding of participants (performance bias)	Low risk	"Randomisation and allocation were performed by persons who were not otherwise involved in the trial."

Blinding of outcome assessment (detection bias)	Low risk	"NCS was performed in an independent laboratory, and the staff did not know anything about the experiment." "The rest of the parts of the examination were conducted by several physiotherapists who did not know anything about patients allocation."
Incomplete outcome data (attrition bias)	Unclear risk	No mention of any attempts to incomplete outcome data.
Selective reporting (reporting bias)	Unclear risk	Authors report that the clinical trial registration number is ACTRN12617000672358, but we could not find the record.
Other sources of biases	Low risk	Not found.
Classification	**High risk**	

Risk of Bias		
Title: Is manual therapy based on neurodynamic techniques effective in the treatment of carpal tunnel syndrome? A randomized controlled trial. Reference: Wolny & Linek, 2019		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation was made before the data collection began using a random number generator computer programme."
Allocation concealment (selection bias)	Low risk	"Those who were randomly assigned '1' were placed in the experimental group, and those who were randomly assigned '2' were placed in the control group."
Blinding of participants (performance bias)	Low risk	"Group assignments were sealed in opaque envelopes. Randomization and allocation were performed by two

		research assistants who were not otherwise involved in the trial."
Blinding of outcome assessment (detection bias)	Low risk	"The nerve conduction study was performed in an independent laboratory as a standard procedure, and staff were not informed about the conducted experiment."
Incomplete outcome data (attrition bias)	Low risk	"The whole protocol accomplished with completed data from 103 participants (Figure 1). Thus, the final analysis involved 103 participants (58 in experimental and 45 in control group)."
Selective reporting (reporting bias)	Low risk	Authors report that the clinical trial registration number is ACTRN12617000672358.
Other sources of biases	Low risk	Not found.
Classification	**Low risk**	

Risk of Bias		
Title: Comparison of two manual therapy techniques in patients with carpal tunnel syndrome: A randomized clinical trial Reference: Talebi et al. 2020		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was carried out by a simple random allocation (figure 1)."
Allocation concealment (selection bias)	High risk	"Patients were alternately assigned to a group as they were identified."
Blinding of participants (performance bias)	Low risk	"The participants were blinded for both grouping and treatment methods."

Blinding of outcome assessment (detection bias)	Low risk	“The examiner collecting the outcome measures before and after treatment procedures and the data analyst were unaware of the assigned treatment.”
Incomplete outcome data (attrition bias)	High risk	“However, 9 patients failed to complete all the outcome measures yielding 30 patients in the final analysis.”
Selective reporting (reporting bias)	Unclear risk	Authors report that the clinical trial registration number is 201508182851N4, but we could not find the record.
Other sources of biases	Low risk	Not found.
Classification	**High risk**	

Capítulo 4 Produto(s) Técnico-Tecnológico(s)

2.1 Curso de formação profissional

2021

1. Corrêa, Leticia Amaral; **Bittencourt, Juliana Valentim;** Telles, Gustavo Felicio; Nogueira, Leandro Alberto Calazans. **Tratamento fisioterápico dos pacientes com dores ciáticas.** 2021. (Curso de curta duração ministrado/Extensão).

2022

2. **Bittencourt, Juliana Valentim;** Rio, Jéssica Pinto Martins; Moreira, Luiza Ferreira. **Avaliação e tratamento fisioterapêutico de pacientes com dor musculoesquelética: o que sabemos?** 2022. (Curso de curta duração ministrado/Extensão).

2.2 Evento organizado

Participou como membro da comissão científica do VII Simpósio Paradesportivo Carioca, que aconteceu em 20 de setembro de 2023, no Centro Universitário Augusto Motta (UNISUAM), Unidade Bonsucesso.

Capítulo 5 Considerações Finais

Os resultados apresentados nesta tese fornecem informações valiosas sobre vários aspectos do manejo da dor e dos cuidados de saúde para pacientes com dores musculoesqueléticas. Essas descobertas têm implicações clínicas importantes para os profissionais de saúde, particularmente os fisioterapeutas, nos seus esforços para melhorar o atendimento ao paciente e as estratégias de tratamento. Ao considerar a letramento em saúde, diagnosticar com precisão os pacientes com dor espalhada e os pacientes com fibromialgia, utilizar ferramentas de avaliação modernas, modelos preditivos e abordagens especializadas para cuidados pós-COVID-19, os clínicos podem adaptar melhor as suas estratégias de tratamento para melhorar os resultados e adesão ao tratamento dos pacientes com dor musculoesquelética. Na prática clínica, tais descobertas incentivam uma abordagem centrada no paciente para o manejo da dor musculoesquelética. Neste capítulo apresentaremos as principais implicações clínicas e recomendações para futuros estudos derivados dos nossos resultados.

5.1 Letramento em saúde e manejo da dor musculoesquelética

O **subtópico 2.2.1** desta tese apresenta o papel crítico do letramento em saúde na queixa musculoesquelética do paciente. Pacientes com letramento em saúde inadequado apresentaram resultados desfavoráveis em termos de intensidade de dor e cinesiofobia. Assim, recomenda-se que os profissionais de saúde priorizem a educação e comunicação com os pacientes, adaptando a sua abordagem aos níveis de letramento em saúde dos pacientes com dor musculoesquelética. Na prática clínica cotidiana, diversas estratégias podem ser adotadas, entre elas, o fornecimento de materiais escritos, o uso de linguagem simples e a garantia de que os pacientes com dor musculoesquelética participem e compreendam seus planos de tratamento fisioterapêutico.

Futuros estudos devem considerar repetir nossa metodologia em larga escala para explorar melhor o impacto do letramento em saúde nos desfechos clínicos, considerando vários ambientes e populações. Tal fato pode ajudar a confirmar nossas descobertas e avaliar a generalização dos resultados. Além disso, é necessário

investigar a eficácia das intervenções destinadas a melhorar o letramento em saúde de pacientes com dores musculoesqueléticas para determinar se o nível adequado de letramento em saúde pode levar a resultados de dor mais favoráveis.

5.2 Fibromialgia versus dor espalhada

O **subtópico 2.2.2** destaca a importância de distinguir os pacientes com fibromialgia daqueles com dor espalhada. Compreender as diferenças nas características da dor, como intensidade da dor, sintomas neuropáticos e sintomas de sensibilização central é crucial para um diagnóstico preciso e abordagens personalizadas. Apesar de apresentarem algumas características similares, a fibromialgia e o paciente com quadro de dor espalhada representam duas condições distintas. Portanto, os clínicos devem estar atentos na identificação do perfil de dor de cada paciente.

Pesquisas futuras devem considerar um acompanhamento longitudinal dos pacientes com fibromialgia e com dor espalhada a fim de compreender melhor a progressão das características da dor. Esse modelo de estudo pode fornecer informações sobre a mudança ou manutenção das características da dor ao longo do tempo e como elas podem afetar os resultados do tratamento fisioterápico. Ademais, os pesquisadores devem considerar explorar possíveis diferenças genéticas ou biomarcadores entre pacientes com fibromialgia e dor espalhada para identificar marcadores biológicos que podem auxiliar no diagnóstico e planejamento do tratamento fisioterapêutico dessas populações.

5.3 Ferramentas para avaliação da dor espalhada

As descobertas no **subtópico 2.2.3** enfatizam uma correlação positiva fraca entre o índice de dor generalizada e o software painMAP para avaliar áreas de dor em pacientes com dor espalhada. Na prática clínica, essas ferramentas para avaliação da dor podem ser benéficas, auxiliando os profissionais a mapear e abordar a dor musculoesquelética de forma mais eficaz em pacientes com dor espalhada.

Pesquisas futuras são necessárias para investigar a confiabilidade e validade das ferramentas de avaliação da dor musculoesquelética, como o software painMAP, em diversas populações de pacientes, tais como, os pacientes com dor espalhada. Tal fato pode ajudar a refinar e aprimorar essas ferramentas para uso clínico.

Ademais, é necessário verificar o potencial de combinação de múltiplas ferramentas de avaliação da dor musculoesquelética a fim de fornecer uma compreensão mais abrangente das experiências de dor dos pacientes com dor musculoesquelética.

5.4 Modelos de Aprendizado de Máquina e Predição para Tratamento da Dor

O **subtópico 2.2.4** apresenta o XGBoost como uma ferramenta potencial para prever a eficácia da modulação condicionada da dor em pacientes com dor musculoesquelética. Essa abordagem de modelagem de predição é promissora para a adoção de estratégias de manejo da dor de acordo com as necessidades individuais do paciente. Outro ponto que podemos destacar é que esse recurso pode auxiliar os clínicos no planejamento e na otimização do tratamento fisioterapêutico com base na probabilidade de o paciente com dor musculoesquelética responder a intervenções específicas.

Novos estudos são necessários a fim de expandir o uso de modelos de aprendizado automático, como o XGBoost, na predição dos desfechos clínicos. Esses modelos são capazes de explorar a interação de dados particulares do paciente, como fatores genéticos, de estilo de vida e histórico de tratamento, a fim de melhorar a acurácia preditiva. Também é necessário investigar a implementação prática de modelos de aprendizado de máquina e avaliar o seu impacto em planos de tratamento personalizados com o objetivo de auxiliar o paciente no gerenciamento da dor musculoesquelética.

5.5 Gerenciamento da dor pós-COVID-19

O **subtópico 2.2.5** fornece um guia prático para fisioterapeutas sobre o tratamento da dor após um episódio de COVID-19. Dado o impacto contínuo da pandemia, os profissionais de saúde devem estar preparados para auxiliar os pacientes que se recuperaram da COVID-19 e permaneceram com alguma condição dolorosa. Nossa carta auxilia na orientação dos profissionais de saúde a respeito da prestação de atendimento especializado a essa população de pacientes.

Futuros estudos são necessários a fim de: a) realizar um acompanhamento a longo prazo de pacientes que se recuperaram da COVID-19 e permaneceram com alguma condição dolorosa para avaliar a persistência dos sintomas relacionados com

a dor e a eficácia de possíveis estratégias de tratamento; b) explorar os fatores psicológicos e sociais que contribuem para as experiências de dor pós-COVID-19.

5.6 Mobilização neural como estratégia de tratamento para dor neuropática periférica

A revisão sistemática no **tópico 3.1** sugere que a mobilização neural pode oferecer benefícios aos pacientes com dor neuropática periférica. Embora a evidência seja de qualidade variável, os fisioterapeutas devem considerar a incorporação de técnicas de mobilização neural nos seus protocolos de tratamento para pacientes com dores neuropáticas. A mobilização neural pode potencialmente levar a melhorias na área de secção transversa, na função motora e na velocidade de condução sensorial nesses pacientes.

Pesquisas futuras são necessárias a fim de investigar os possíveis protocolos de atendimento para esses pacientes, considerando a duração e a frequência das técnicas de mobilização neural para diferentes subtipos de dor neuropática periférica. Os pesquisadores devem realizar ensaios clínicos randomizados de alta qualidade para fornecer evidências mais fortes da eficácia da mobilização neural em pacientes com dor neuropática periférica. Novos estudos também podem comparar a eficácia da mobilização neural com outras intervenções não farmacológicas para o controle da dor neuropática periférica (fisioterapia, programas de exercícios ou terapia cognitivo-funcional). Além disso, é fundamental avaliar a relação custo-benefício/eficácia da mobilização neural em termos de recursos de saúde e resultados para os pacientes com dor neuropática periférica.

As recomendações apresentadas nessa tese orientam os futuros estudos a atestarem a nossa compreensão do tratamento da dor musculoesquelética em vários contextos clínicos e a melhorar a qualidade do atendimento aos pacientes que sofrem com alguma condição de dor musculoesquelética.

Acurácia diagnóstica dos indicadores clínicos para identificar a dor de sensibilização central em pacientes com dor musculoesquelética

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Resumo

Fundamento: A identificação da Sensibilização Central (SC) é um aspecto importante no manejo de pacientes com dor crônica musculoesquelética. Diversos métodos têm sido desenvolvidos, incluindo indicadores clínicos e medidas psicofísicas. Entretanto, ainda é incerto se indicadores clínicos coincidem com o teste psicofísico de sinais e sintomas relacionados à SC. Portanto, o presente estudo tem o objetivo de analisar a acurácia diagnóstica dos indicadores clínicos na identificação de sinais e sintomas relacionados à SC em pacientes com dor musculoesquelética.

Métodos: foram incluídos cem pacientes consecutivos com dor musculoesquelética. Indicadores clínicos (método-índice), baseados numa combinação de características de dor autorreportadas pelo paciente e o exame físico, foram usados para identificar o fenótipo de pacientes com dor musculoesquelética e predominância de sinais e sintomas relacionados à SC. A Modulação Condicionada de Dor foi avaliada através do *Cold Pressor Test* (padrão de referência), um teste psicofísico usado para detectar deficiência da Modulação Condicionada de Dor. Medidas de acurácia diagnóstica foram realizadas.

Resultados: Vinte e sete pacientes apresentaram predominância de sinais e sintomas relacionados à SC na avaliação dos indicadores clínicos, e 20 tinham uma Modulação Condicionada de Dor prejudicada. Os indicadores clínicos demonstraram alta acurácia (75,0%; intervalo de confiança 95% = 65,3 a 83,1), alta especificidade (80,0%; intervalo de confiança 95% = 69,6 a 88,1), alto valor preditivo negativo (87,7%; intervalo de confiança 95% = 81,2 a 92,1) e uma razão de verossimilhança positiva relevante (2,8; intervalo de confiança 95% = 1,5 a 5,0) quando comparados ao *Cold Pressor Test*.

Conclusão: Indicadores clínicos demonstraram ser uma ferramenta valiosa para detectar a deficiência da Modulação Condicionada de Dor, a qual representa uma característica marcante dos sinais e sintomas relacionados à SC. Clínicos são encorajados a utilizar os indicadores clínicos no manejo de pacientes com dor musculoesquelética.

Palavras-chave: dor musculoesquelética, dor crônica, mecanismos de dor, sensibilização do sistema nervoso central, controle inibitório nocivo difuso; limiar de dor, manejo da dor.

O artigo no original, Bittencourt, J.V., de Melo Magalhães Amaral, A.C., Rodrigues, P.V. *et al.* Diagnostic accuracy of the clinical indicators to identify central sensitization pain in patients with musculoskeletal pain. *Arch Physiother* **11,** 2 (2021). https://doi.org/10.1186/s40945-020-00095-7, de acesso aberto e disponível em: https://archivesphysiotherapy.biomedcentral.com/articles/10.1186/s40945-020-00095-7, é protegido por direitos autorais e foi disponibilizado na rede mundial de computadores através da licença Creative Commons CC-BY (https://creativecommons.org/licenses/by/4.0/). Este artigo foi traduzido por Annemarie Frank e a tradução revisada por Marcelo Paiva. A tradução também é protegida por direitos autorais e está disponível através da Licença Creative Commons CC-BY-NC https://creativecommons.org/licenses/by-nc/4.0).

Fundamento

Condições de saúde musculoesquelética são uma causa comum de dor na população geral, e a Sensibilização Central (SC) está ligada a um número desses pacientes. A dor musculoesquelética está presente em aproximadamente a metade da população da Europa [1], dos Estados Unidos [2] e do Brasil [3]. Pessoas com condições de saúde musculoesquelética podem desenvolver uma condição de dor crônica que afeta aproximadamente 40% da população mundial [4]. Um estudo evidenciou que 41% dos brasileiros têm dor com mais de 6 meses de duração [5]. A característica persistente da dor tem sido associada à SC. Diversos estudos em pacientes com dor musculoesquelética revelaram as implicações da SC na percepção de dor em pacientes com condições musculoesqueléticas [6-9]. Uma revisão narrativa revelou que essas condições foram categorizadas como psicossomáticas, funcionais, somatizações e desordens médicas inexplicadas [10]. Previamente, Yunus propôs o termo "Síndrome de SC" para desordens não orgânicas que compartilham várias características em comum, incluindo dor e fatores psicossociais [11].

A identificação da dor relacionada à SC é um desafio clínico para profissionais de saúde, pois não existe um método de avaliação padrão-ouro [12]. Além disso, a definição de SC permanece incerta. De acordo com Woolf, SC é definida como a "amplificação da sinalização neural dentro do sistema nervoso central que provoca hipersensibilidade de dor" [6]. Outros autores argumentam que a SC abrange a Modulação Condicionada de Dor [13] e a ativação de vias facilitadoras de dor descendentes e ascendentes [14]. Algumas ferramentas estão disponíveis para identificar os pacientes com dor musculoesquelética relacionada à SC, sendo que a Modulação Condicionada de Dor é a mais utilizada para esse fim. Modulação Condicionada de Dor ocorre quando um estímulo condicionante [p.ex. o *Cold Pressor Test* (CPT)[1], que envolve a imersão da mão em água fria] inibe o estímulo doloroso. Embora o CPT tenha sido o método mais comumente usado para a avaliação da Modulação Condicionada de Dor [15], esse teste psicofísico pode ser pouco prático para uma triagem clínica de rotina, pois necessita de aparelhos específicos (p.ex. termômetro, um recipiente com gelo e um algômetro de pressão). Enquanto isso, indicadores clínicos englobam um conjunto de informações coletadas durante a avaliação clínica regular. Contudo, não se sabe se a Modulação Condicionada de Dor é deficiente em pacientes com o fenótipo clínico de SC.

A frequência importante de pacientes com dor crônica musculoesquelética e a predominância do fenótipo de SC [16] levaram pesquisadores a propor ferramentas para a identificação desse fenótipo clínico [7, 17-19]. Profissionais de saúde desenvolveram uma lista, baseada em consenso, de sinais e sintomas (indicadores clínicos) sugestivos para cada mecanismo de dor (nociceptiva, neuropática periférica ou SC) [20]. Logo, indicadores clínicos, baseados numa combinação de características da dor autorrelatadas pelo paciente e do exame físico, foram descritos para identificar o mecanismo da dor musculoesquelética [20]. Um estudo anterior confirmou a validade discriminante para a identificação de cada dominância de dor em pacientes com dor lombar [19]. Os indicadores clínicos demonstraram alta confiabilidade em pacientes com dor lombar [21] e pacientes com dor cervical inespecífica [22]. Além disso,

[1] n.t.: Teste Pressório ao Frio

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indicadores clínicos têm sido recomendados para o manejo de dor lombar [9], dor inespecífica do ombro [23] e dor crônica relacionada à osteoartrite [24]. Embora os indicadores clínicos sejam baseados na perspectiva de clínicos, nosso grupo encontrou uma prevalência similar de pacientes com sinais e sintomas relacionados à SC (21%) [16] e Modulação Condicionada de Dor comprometida (25%) [25] em pacientes com dor musculoesquelética. Dessa forma, existe a necessidade de verificar se os indicadores clínicos são acurados para detectar a deficiência de Modulação Condicionada de Dor.

A falta de terminologia robusta para identificar características clínicas e mecanismos neurofisiológicos dificultam a tomada de decisão clara em pacientes com dor crônica musculoesquelética. Indicadores clínicos têm o potencial de ser uma ferramenta adequada para objetivos de triagem, além de serem úteis para guiar o manejo de pacientes com dores variadas. Ainda assim, é preciso uma investigação da validade de critério dos indicadores clínicos (método-índice) para detectar a deficiência de Modulação Condicionada de Dor usando um teste psicofísico (padrão de referência), a fim de garantir uma classificação adequada dos pacientes. Desta maneira, o presente estudo tem por objetivo analisar a acurácia diagnóstica dos indicadores clínicos na identificação da deficiência de Modulação Condicionada de Dor em pacientes com dor musculoesquelética. Nossa hipótese é de que pacientes de dor musculoesquelética que apresentam fenótipo clínico de sinais e sintomas relacionados à SC apresentem um comprometimento da Modulação Condicionada de Dor.

Métodos

Desenho do estudo e considerações éticas

Esse estudo de acurácia diagnóstica seguiu o *Standards for Reporting Studies of Diagnostic Accuracy* (STARD) [26]. O estudo foi aprovado pelo Comitê de Ética em Pesquisa do Centro Universitário Augusto Motta (Número CAAE: 46245215.9.0000.5235), seguindo a Declaração de Helsinki para pesquisas em humanos. Todos os pacientes que preencheram os critérios de eligibilidade assinaram um formulário de consentimento informado antes dos procedimentos do estudo.

Pacientes do estudo

Pacientes consecutivos com dor musculoesquelética (com idade de 18 anos e mais) do setor de fisioterapia ambulatorial do Hospital Universitário Gaffrée e Guinle foram cadastrados enquanto buscavam tratamento entre novembro de 2015 e maio de 2016. O estudo incluiu pacientes com dor aguda (duração de dor menor do que 3 meses) e dor crônica (duração de dor maior do que 3 meses). Dor musculoesquelética foi definida como a dor percebida numa região do corpo com origem muscular, ligamentar, óssea ou articular [2]. O estudo excluiu pacientes que tiveram procedimento cirúrgico na coluna, mulheres grávidas, pacientes com diagnósticos reumatológicos em fase inflamatória aguda, com tumores, analfabetos ou que não completaram os questionários de autorrelato.

Procedimentos

Os pacientes foram encaminhados para uma avaliação inicial que consistia na tomada da história clínica e no exame físico. A aquisição de informações sociodemográficas e clínicas foi realizada por um instrumento contendo dados demográficos (nome completo, gênero, idade, endereço, grau de escolaridade, ocupação, estado civil), características da dor musculoesquelética (localização da dor, intensidade da dor, duração da dor) e o comportamento de exercício físico. Os participantes completaram os itens relacionados aos indicadores clínicos para a predominância da dor musculoesquelética baseada em seu

mecanismo [19], que classifica os pacientes em sinais e sintomas nociceptivos, neuropáticos periféricos ou relacionados à SC. Então, os participantes foram instruídos a realizar o teste psicofísico, conduzido no mesmo dia.

A intensidade de dor foi medida usando-se a Escala Numérica de Dor (END) de 0 a 10 (ou seja, 0 significa sem dor e 10, a pior dor possível). A duração da dor foi registrada em meses, e os pacientes foram classificados como tendo dor crônica musculoesquelética se tivessem tido dor por mais de 3 meses, de acordo com a definição da *International Association for the Study of Pain* [27]. O comportamento de exercício físico foi autorrelatado, sendo definido como uma forma de atividade física planejada, estruturada, repetitiva e com o objetivo de melhorar ou manter o condicionamento físico [28]. O preenchimento dos formulários demorou aproximadamente 10 minutos por participante e foi supervisionado por um avaliador para esclarecimento em caso de dúvidas.

Instrumentos de medida

Fenótipo clínico de SC

A classificação de dor musculoesquelética em dor nociceptiva, dor neuropática periférica e sinais e sintomas relacionados à SC foi identificada baseando-se no reconhecimento de indicadores clínicos, que utilizam uma combinação de características de dor autorrelatadas pelo paciente e exame físico. O exame físico incluiu avaliações musculoesqueléticas e neurológicas. Dois fisioterapeutas realizaram a classificação da predominância de dor musculoesquelética. Os dois fisioterapeutas envolvidos (L.A.C.N. e F.J.J.R.) possuíam 16 anos de experiência de trabalho num departamento ambulatorial no tratamento de pacientes com desordens musculoesqueléticas. Um procedimento padronizado foi definido por um avaliador (L.A.C.N.), que também forneceu uma sessão de 3 horas de treinamento para o protocolo de avaliação ao outro (F.J.J.R.), a fim de esclarecer e confirmar a compreensão do procedimento de avaliação. Quaisquer dúvidas que surgiram durante esse processo foram resolvidas através do consenso entre os dois avaliadores. Os seguintes indicadores definiram a predominância de cada dor musculoesquelética:

Sensibilização Central: Uma dominância de sinais e sintomas relacionados à SC foi considerada usando um conjunto de quatro critérios, como descrito previamente na literatura [19]: (1) dor desproporcional à natureza e extensão da lesão ou patologia; (2) um padrão de provocação de dor desproporcional, não mecânico, imprevisível, em resposta a múltiplos/inespecíficos fatores agravantes/atenuantes; (3) uma forte associação com fatores psicossociais mal-adaptativos, e (4) um sinal (áreas de dor/sensibilidade à palpação difusas/não anatômicas). O conjunto de quatro critérios demonstrou uma sensibilidade de 91,8% e uma especificidade de 97,7% quando comparado ao julgamento clínico de profissional experiente [19].

Dor nociceptiva: O conjunto de sete critérios incluiu a presença/ausência de sintomas. Presença de (1) dor geralmente intermitente e aguda com provocação de movimento/mecânica; durante o repouso, possivelmente dor mais constante, surda ou latejante; (2) dor localizada na área da lesão/disfunção; (3) dor de natureza mecânica/anatômica clara, proporcional a fatores agravantes e atenuantes. Ausência de (1) dor com descrição variada como queimação, fuzilante, facada ou como choque elétrico, (2) dor em associação a outras disestesias, (3) dor noturna/sono perturbado; e (4) um sinal (postura/padrão de movimento antálgico) [19]. Uma dominância de dor nociceptiva foi prevista pelo conjunto de sete critérios com uma sensibilidade de 90,9% e uma especificidade de 91,0% quando

comparado a um julgamento clínico de profissional experiente [19].

Dor neuropática periférica: O conjunto de três critérios incluiu a presença de três características: (1) história de lesão, patologia ou comprometimento mecânico neural; (2) dor referida em distribuição dermatomal ou cutânea, e (3) provocação da dor/sintoma com testes mecânicos/de movimento. Uma avaliação física neurológica foi baseada no exame neurológico clássico, que foi realizado para confirmar a dor periférica neuropática, e então, a distribuição dermatomal da dor. Testes de força muscular, testes neurodinâmicos (ou seja, slump, ciático, femoral, mediano, ulnar e radial) e testagem da função das fibras sensoriais foram conduzidos para confirmar a hipótese [19]. Uma dominância de dor neuropática periférica foi encontrada pelo conjunto de três critérios com uma sensibilidade de 86,3% e uma especificidade de 96,0% quando comparado a um julgamento clínico de profissional experiente [19].

Característica neurofisiológica da SC

Modulação Condicionada de Dor – o *Cold Pressor Test* (CPT) foi o teste psicofísico usado para mensurar a Modulação Condicionada de Dor. O CPT usa o estímulo condicionante de dor para medir a Modulação Condicionada de Dor, o que é um método adequado para avaliar o sistema inibitório nociceptivo descendente [5]. O estímulo condicionante foi a imersão da mão não dominante, assintomática, do participante num balde com água fria de temperatura controlada (1°C - 4°C), monitorada por um termômetro (Modelo 5130, Incoterm), por até 1 minuto. O participante foi instruído a permanecer com a mão imersa na água sem realizar contrações musculares ou alterar a posição. A retirada da mão da água foi permitida quando o paciente não conseguia mais tolerar o estímulo doloroso. A temperatura da sala, umidade, iluminação e ruído foram mantidos constantes durante todo o procedimento.

O Limiar de Dor à Pressão foi realizado nas regiões do antebraço e do músculo tibial anterior dos membros dominantes antes e depois de 1 minuto do CPT, usando um algômetro digital de pressão (Modelo Force Ten FDX, Wagner Instruments, Greenwich, EUA). Foram escolhidos para avaliação o músculo tibial anterior e a parte distal do antebraço dorsal, que não estiveram imersos na água, devido à ausência de relação com as queixas musculoesqueléticas dos participantes. O manejo do algômetro de pressão e a mensuração do Limiar de Dor à Pressão foram explicados aos pacientes antes da avaliação. Além disso, um procedimento de familiarização ao algômetro de pressão foi realizado aplicando-se pressão ao antebraço dominante para garantir que o teste fosse bem compreendido. A força era gradualmente aumentada (1kg-força/s) até que a sensação de pressão do participante mudasse para dor. O Limiar de Dor à Pressão era registrado em quilogramas-força (Kgf) quando o paciente dava o comando verbal "dor".

Somente pacientes com uma ineficiência da Modulação Condicionada de Dor em ambos os locais (músculo tibial anterior e parte distal do antebraço dorsal) foram classificados como Modulação Condicionada de Dor prejudicada. Foram utilizados locais no membro superior e inferior para evitar a inclusão de pacientes com sensibilização periférica, de acordo com as recentes recomendações para a Modulação Condicionada de Dor [29]. Além disso, a eficiência do sistema inibitório nociceptivo descendente foi avaliada através do cálculo da diferença entre os valores do Limiar de Dor à Pressão no CPT (valor final - valor inicial). Valores negativos representaram uma ineficiência do sistema inibitório nociceptivo descendente, e valores nulos ou positivos foram

considerados uma resposta típica do sistema inibitório nociceptivo descendente.

Análise estatística

As variáveis demográficas e clínicas da população do estudo foram apresentadas como médias e desvios-padrão para variáveis contínuas. Variáveis categóricas foram apresentadas como valores absolutos e frequências. O teste de Shapiro-Wilk verificou a distribuição normal da maioria das variáveis contínuas. Nós comparamos o grupo de pacientes que apresentou deficiência da Modulação Condicionada de Dor com aqueles sem deficiência da Modulação Condicionada de Dor. A acurácia diagnóstica dos indicadores clínicos (método-índice) foi comparada com a medida psicofísica (padrão de referência). Nós calculamos sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo, acurácia diagnóstica, razões de verossimilhança positiva e negativa. Os resultados estão apresentados com o respectivo intervalo de confiança 95% (IC 95%). Foi considerado um nível de significância de menos de 5% ($P < 0,05$) para todas as análises. A análise estatística foi realizada usando o SSPS versão 20.0 (IBM Corporation, Armonk, New York).

Resultados

Características dos participantes

O estudo foi composto por 100 pacientes com dor musculoesquelética, sendo 27 deles homens e 73 mulheres, com uma média de idade de 50,9 (±16,6) anos. Doze (10,08%) participantes foram classificados com dor aguda e 88 (73,95%) com dor crônica. A média de peso foi de 72,9 (±15,4) kg, e a massa corporal média foi de 25,9 (±5,2) kg/m^2. Em relação à característica de dor, a intensidade média da dor foi de 6,0 (±2,5), e a duração média da dor foi de 43,0 (±53,0) meses. Todos os participantes completaram a classificação dos sinais e sintomas relacionados à SC usando os indicadores clínicos e o teste CPT. Não houve, portanto, valores ausentes para nenhuma das classificações. Não houve eventos adversos associados aos questionários e ao teste psicofísico.

Identificação da SC

Entre todos os participantes, 27 apresentaram o fenótipo clínico de sinais e sintomas relacionados à SC, enquanto 20 apresentaram deficiência da Modulação Condicionada de Dor, 16 dos quais (80%) foram mulheres. Quatorze (14%) pacientes foram classificados como dor aguda musculoesquelética e 86 (86%) como dor crônica musculoesquelética. A deficiência da Modulação Condicionada de Dor foi observada em 4 (29%) pacientes com dor aguda musculoesquelética e em 16 (19%) pacientes com dor crônica musculoesquelética. Um teste Qui-quadrado revelou proporções similares de deficiência da Modulação Condicionada de Dor entre os grupos ($X^2 = 0.748$; $p = 0.387$). Não houve diferenças significantes nas características clínicas e demográficas entre os dois grupos, e os dados estão demonstrados na Tabela 1.

A Tabela 2 apresenta os valores do Limiar de Dor à Pressão para a região dorsal do antebraço e o tibial anterior dos participantes. O Limiar de Dor à Pressão sobre o antebraço dorsal esteve reduzido nos participantes com deficiência de Modulação Condicionada de Dor na avaliação pós-teste [Modulação Condicionada de Dor deficiente = 2,6 (±0,78), Modulação Condicionada de Dor normal = 5,4 (±2,5); $p< 0,001$)], assim como na região tibial anterior [(Modulação Condicionada de Dor deficiente = 4,0 (±2,2), Modulação Condicionada de Dor normal = 6,7 (±3,4); $p< 0,001$)]. Consequentemente, a comparação intra-grupo também foi estatisticamente significante (Tabela 2).

Tabela 1 Características clínicas e demográficas dos participantes do estudo (*n* = 100)

Características	Modulação Condicionada de Dor deficiente (*n* = 20)	Modulação Condicionada de Dor normal (*n* = 80)	Valor *P*
Idade, média (DP)	55,3 (16,67)	49,8 (16,6)	0,195
Gênero, n (%), mulheres	16 (80%)	57 (71%)	0,430
Índice de Massa Corporal, média (DP)	25,4 (3,17)	26,1 (3,17)	0,713
Exercício físico (Sim), n (%)	5 (25%)	39 (48%)	0,056
Comorbidades, média (DP)	0,9 (0,90)	0,8 (1,1)	0,824
Duração da dor (meses), média (DP)	41,1 (48,5)	43,5 (54,4)	0,855
Intensidade da dor, média (DP)	7,0 (2,7)	5,8 (2,4)	0,090
Localização da dor, n (%)			0,603
Dor cervical	-	5 (6%)	
Dor torácica	-	-	
Dor lombar	1 (5%)	13 (16%)	
Dor de cabeça	-	1 (1%)	
Dor no membro superior	3 (15%)	7 (8%)	
Dor no membro inferior	3 (15%)	12 (15%)	
Mais de um local	9 (45%)	35 (43%)	
Fenótipo de dor, n (%)			0,001
Sensibilização Central	11 (55%)	16 (20%)	
Nociceptiva	8 (40%)	31 (39%)	
Neuropática Periférica	1 (5%)	33 (41%)	

Nota: Dados são apresentados como médias (DP) para variáveis contínuas e como contagem de frequências (%) para variáveis categóricas. Diferenças significantes entre grupos foram testadas usando o teste-t não pareado para variáveis contínuas ou o teste Qui-quadrado para variáveis categóricas

Tabela 2 Valores do Limiar de Dor à Pressão para regiões do antebraço dorsal e tibial anterior dos pacientes com desordens musculoesqueléticas (*n* = 100)

Característícas	Modulação Condicionada de Dor deficiente (*n* = 20)	Modulação Condicionada de Dor normal (*n* = 80)	Valor *P*
Linha de base			
Algometria antebraço dorsal (kgf)	3,0 (0,8)	3,5 (1,8)	0,189
Algometria tibial anterior (kgf)	5,0 (2,8)	5,1 (2,3)	0,792
Após *Cold Pressor Test*			
Algometria antebraço dorsal (kgf)	2,6 (0,8)	5,4 (2,5)	< 0,001*
Algometria tibial anterior (kgf)	4,0 (2,2)	6,7 (3,4)	< 0,001*
Variação intragrupo			
Algometria antebraço dorsal (kgf)	−0,3 (0,5)	1,8 (1,3)	< 0,001*
Algometria tibial anterior (kgf)	−0,9 (1,6)	1,5 (2,2)	< 0,001*

Nota: Dados são apresentados como médias (DP). Diferenças significantes entre grupos foram testadas usando o t-teste não pareado. *Representa valores *P* significantes (*P*< 0,05)

Acurácia diagnóstica dos indicadores clínicos

Os indicadores clínicos demonstraram alta especificidade (80,0%; IC 95% 69,6 a 88,1), alta acurácia (75,0%; IC 95% = 65,3 a 83,1), alto valor preditivo negativo (87,7%; IC 95% = 81,2 a 92,1) e uma razão de verossimilhança positiva relevante (2,8, IC 95% = 1,5 a 5,0), mas baixos valores de sensibilidade (55,0%; IC 95% = 31,5 a 76,9) e valor preditivo positivo (40,7; IC 95% = 27,6 a 55,4) quando comparados ao CPT. Medidas de sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo e acurácia para o diagnóstico de sensibilização central estão apresentados na Tabela 3.

Tabela 3 Valores de sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo, acurácia, prevalência da doença e razões de verossimilhança (positiva e negativa) do diagnóstico clínico de sinais e sintomas relacionados à SC

	Diagnóstico clínico
Sensibilidade %, (IC 95%)	55,0 (31,5 a 76,9)
Especificidade %, (IC 95%)	80,0 (69,6 a 88,1)
Valor preditivo positivo (VPP) %, (IC 95%)	40,7 (27,6 a 55,4)
Valor preditivo negativo (VPP) %, (IC 95%)	87,7 (81,2 a 92,1)
Acurácia % (IC 95%)	75,0 (65,3 a 83,1)
Prevalência da doença %, (IC 95%)	20,0 (12,7 a 29,2)
Razão de verossimilhança positiva (RV+) (IC 95%)	2,8 (1,5 a 5,0)
Razão de verossimilhança negativa (RV-) (IC 95%)	0,6 (0,3 a 0,9)

Nota: Abreviações: *IC* Intervalo de Confiança, *VPP* Valor preditivo positivo, *VPN* Valor preditivo negativo, *RV+* Razão de verossimilhança positiva, *RV-* Razão de verossimilhança negativa

Discussão

Esse estudo investigou a acurácia diagnóstica dos indicadores clínicos na identificação de pacientes com dor musculoesquelética e sinais e sintomas relacionados à SC, considerando a deficiência de Modulação Condicionada de Dor como o padrão mensurado. Indicadores clínicos demonstraram altos valores de acurácia diagnóstica, especificidade e valor preditivo negativo do diagnóstico clínico de deficiência de Modulação Condicionada de Dor em pacientes com dor musculoesquelética. Além disso, a razão de verossimilhança positiva encontrada no estudo atual representa um aumento relevante em probabilidades favorecendo uma regra em pacientes com Modulação Condicionada de Dor comprometida. Os indicadores clínicos demonstraram utilidade para detectar a deficiência de Modulação Condicionada de Dor em pacientes com dor musculoesquelética, especialmente para excluir aqueles pacientes que não possuem Modulação Condicionada de Dor prejudicada.

Nós reconhecemos pontos fortes e limitações no estudo atual. O primeiro ponto forte é a novidade de validar a utilização de um sistema prático e objetivo para a identificação clínica do fenótipo de pacientes com sinais e sintomas relacionados à SC. O segundo ponto forte foi o uso de um método psicofísico para a identificação da deficiência de Modulação Condicionada de Dor usando dois locais anatômicos distintos para a sua classificação. Por fim, nós registramos pacientes alvo-positivos e alvo-negativos (ou seja, pacientes com dor musculoesquelética com e sem sinais e sintomas relacionados à SC) da mesma população numa amostragem de pacientes consecutivos. Em relação às limitações do estudo, o CPT não é o padrão-ouro para a identificação do comprometimento da Modulação Condicionada de Dor. Um experimento com hiperalgesia secundária induzida por injeção intradérmica de capsaicina é exigido para a confirmação de SC [30]. Mesmo assim, o CPT é o método mais comumente utilizado para a avaliação da Modulação Condicionada de Dor [15], representando um método apropriado para avaliar o sistema inibitório nociceptivo descendente [31] e um

componente da SC. O número de participantes inscritos no estudo atual pode ser insuficiente para objetivos de validação, e uma amostra maior seria necessária. Todavia, um tamanho amostral total igual ou maior a 100 participantes tem sido considerado um aspecto para um nível de evidência forte em estudos de propriedades de medida [32-34]. Estudos de validação são representativos da amostra estudada, e nossos resultados precisam ser testados em diferentes populações para a generalização dos achados. Por fim, nós não controlamos o uso de medicação analgésica, o que pode afetar a resposta da Modulação Condicionada de Dor, apesar dos resultados contraditórios descritos numa revisão sistemática [35].

Apesar da alta proporção de participantes sem sinais e sintomas relacionados à SC corretamente diagnosticados (ou seja, valor preditivo negativo), a razão de verossimilhança negativa não foi pequena o suficiente para excluir os sinais e sintomas relacionados à SC com segurança. Valores preditivos fornecem probabilidades de anormalidade para um teste em particular, mas a prevalência da anormalidade na amostra do estudo interfere com os resultados. No estudo atual, a prevalência de sinais e sintomas relacionados à SC foi de 27%, corroborando um estudo brasileiro prévio [16] e outros estudos internacionais [36]. Assim, a prevalência relativamente baixa de sinais e sintomas relacionados à SC na probabilidade pré-teste influenciou os resultados da razão de verossimilhança, o que gerou uma alteração pequena, mas importante na probabilidade pós-teste da identificação clínica dos sinais e sintomas relacionados à SC. Nossos achados revelaram que pacientes com deficiência de Modulação Condicionada de Dor foram 2,8 vezes mais suscetíveis a terem sinais e sintomas relacionados à SC nos indicadores clínicos do que pacientes com Modulação Condicionada de Dor preservada. O achado notável da razão de verossimilhança positiva representa que os indicadores clínicos são úteis em detectar pacientes com sinais e sintomas relacionados à SC. Dessa forma, os indicadores clínicos representam uma ferramenta rápida de triagem para auxiliar clínicos na identificação de pacientes com predominância de sinais e sintomas relacionados à SC, mas não devem ser usados como ferramenta única.

Nossos achados indicam que indicadores clínicos são uma ferramenta acurada para a identificação dos sinais e sintomas relacionados à SC. Embora a maioria dos pacientes com Modulação Condicionada de Dor prejudicada apresentou sinais e sintomas relacionados à SC, 20% dos participantes apresentaram resultados divergentes. Sendo assim, a apresentação clínica dos sinais e sintomas relacionados à SC em pacientes com dor musculoesquelética pode ser discrepante em relação ao teste psicofísico, que pode revelar o comprometimento neurofisiológico. O diagnóstico conflitante dos sinais e sintomas relacionados à SC na apresentação clínica e no teste neurofisiológico inviabilizam a tomada de decisão adequada em pacientes com dor musculoesquelética. Além disso, os indicadores clínicos foram desenvolvidos para identificar a predominância de dor em pacientes com dor lombar [20]. Consequentemente, pacientes com predominância de dor nociceptiva ou neuropática periférica podem também apresentar uma deficiência do sistema inibitório nociceptivo descendente. Por exemplo, os resultados do estudo de Fingleton e col. [37] demonstraram a presença de SC em pacientes com osteoartrite de joelho, a qual é regularmente considerada como dor nociceptiva. Apesar dessas limitações, nossos resultados evidenciam que pacientes sem a predominância de sinais e sintomas relacionados à SC não apresentam deficiência de Modulação Condicionada de Dor.

Poucos estudos investigaram a validade de ferramentas clínicas para identificar pacientes com sinais e sintomas relacionados à SC. Por exemplo, Gervais-Hupe e col. observaram uma sensibilidade de 87,2% e especificidade de 34,2% na identificação de SC usando o Inventário de Sensibilização Central com ponto de corte de 22 em pacientes com osteoartrite de joelho quando comparado ao CPT [38]. O mesmo estudo demonstrou que o *painDETECT* teve uma sensibilidade de 61,5% e especificidade de 77,6% na identificação de SC usando um ponto de corte de 12 [38]. Dessa forma, o Inventário de Sensibilização Central pode representar um instrumento adequado para identificar pacientes com SC. Em contraste, os indicadores clínicos e o *painDETECT* são ferramentas apropriadas para excluir esses pacientes. Estudos futuros devem se concentrar em métodos para caracterizar de forma pragmática os pacientes com sinais e sintomas relacionados à SC, a fim de facilitar a tomada de decisão dos clínicos.

Conclusão

Indicadores clínicos demonstraram ser uma ferramenta valiosa para detectar a deficiência de Modulação Condicionada de Dor, o que é uma característica marcante de sinais e sintomas relacionados à Sensibilização Central. Clínicos são encorajados a usar os indicadores clínicos no manejo de pacientes com dor musculoesquelética.

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Consentimento informado
Foi obtido o consentimento informado de todos os indivíduos incluídos nesse estudo.

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Todos os pacientes que atenderam aos critérios de elegibilidade assinaram o termo de consentimento informadoantes dos procedimentos do estudo.

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Os autores declaram não haver conflitos de interesse.

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Uso do painDETECT para distinguir fenótipos de dor musculoesquelética

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Resumo

Fundamento: Pacientes com dor musculoesquelética, independentemente do diagnóstico clínico, apresentam características de dor semelhantes. O questionário painDETECT é útil para rastrear sintomas do tipo neuropático em muitas condições musculoesqueléticas. Contudo, nenhum estudo anterior comparou os fenótipos de dor de pacientes com dor musculoesquelética usando o painDETECT. Portanto, o presente estudo teve como objetivo comparar as características da dor de pacientes com dor musculoesquelética classificados de acordo com o painDETECT como dor nociceptiva, indefinida e sintomas do tipo neuropático.

Métodos: Foi realizado um estudo transversal em 308 participantes com dor musculoesquelética. As características demográficas e clínicas dos participantes foram examinadas. Sintomas do tipo neuropático, intensidade da dor, área da dor, sinais e sintomas relacionados à Sensibilização Central, limitação funcional e modulação condicionada da dor foram avaliados em pacientes com dor musculoesquelética. A análise de variância unidirecional independente (ANOVA) foi usada para testar as diferenças entre os grupos para as medidas de desfecho com variáveis contínuas, e o teste qui-quadrado de Pearson verificou as diferenças entre os grupos na eficiência da modulação condicionada de dor.

Resultados: Os participantes tinham uma média de idade de 52,21 (±15,01) anos, e 220 deles (71,42%) eram do sexo feminino. Cento e setenta e três (56,16%) participantes apresentaram dor nociceptiva, 69 (22,40%) indefinida e 66 (21,42%) sintomas do tipo neuropático. Uma ANOVA de uma via mostrou diferenças para a intensidade da dor [$F(2.305) = 20{,}097$; $p < 0{,}001$], área de dor [$F(2.305) = 28{,}525$; $p < 0{,}001$], sinais e sintomas relacionados à Sensibilização Central [$F(2.305) = 54{,}186$; $p < 0{,}001$] e limitação funcional [$F(2.256) = 8{,}061$; $p < 0{,}001$]. No entanto, a modulação condicionada da dor estava comprometida de forma semelhante entre os três grupos ($X^2 = 0{,}333$, $p = 0{,}847$).

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Conclusão: Os pacientes com sintomas do tipo neuropático, quando comparados aos seus pares, revelaram características de dor desfavoráveis, incluindo a intensidade da dor, dor generalizada, sinais e sintomas relacionados à Sensibilização Central e limitação funcional.

Palavras-chave: Dor musculoesquelética, Dor neuropática, Mecanismos da dor, Sensibilização do sistema nervoso central, Controle inibitório nocivo difuso

Fundamento

Condições musculoesqueléticas representam uma causa frequente de dor e incapacidade na população mundial. Na Europa, nos Estados Unidos e no Brasil, aproximadamente metade da população é afetada por dor musculoesquelética não inflamatória [1-3]. Pacientes com dor musculoesquelética podem apresentar características de dor semelhantes, independentemente do diagnóstico clínico. Embora a dor musculoesquelética represente um grupo heterogêneo, as condições musculoesqueléticas de diferentes locais anatômicos compartilham características semelhantes de dor [4]. Além disso, cinco fenótipos de dor musculoesquelética foram descritos independentemente da localização primária da dor [5]. Assim, classificar pacientes com dor musculoesquelética pode ser um desafio para os profissionais de saúde.

Dor nociceptiva e neuropática são comumente relatadas por pacientes com dor musculoesquelética. Algumas condições de dor musculoesquelética classificadas como dor nociceptiva (por exemplo, osteoartrite do joelho [6], rupturas do manguito rotador [7] e síndrome do impacto do ombro [8]) podem apresentar sintomas do tipo neuropático. Embora haja um intercâmbio de várias características de dor que classificam a predominância de dor nociceptiva ou de sintomas neuropáticos, estudos anteriores mostraram que pacientes com sintomas do tipo neuropático tiveram desfechos desfavoráveis [9-13]. Aumento da dor e incapacidade, baixa qualidade de vida e aumento do uso de recursos de saúde, por exemplo, são mais relatados por pacientes com dor lombar irradiada para a perna do que em pacientes com dor lombar isolada [9]. Além disso, outros estudos relataram dor mais intensa, pior saúde física, sintomas de depressão e sofrimento psicológico associados a sintomas do tipo neuropático quando comparados a pacientes com dor nociceptiva [10-13]. Portanto, é essencial verificar as divergências das características da dor presentes nessas condições de dor musculoesquelética.

Diversas ferramentas têm sido utilizadas na avaliação de pacientes com dor musculoesquelética[1]. O Inventário de Sensibilização Central (*Central Sensitization Inventory* - CSI) é o questionário mais usado para identificar sinais e sintomas relacionados à Sensibilização Central (SC) [14]. Pacientes com osteoartrite de joelho, que é regularmente considerada como dor nociceptiva, apresentam sinais e sintomas relacionados à SC [15]. Da mesma forma, sinais e sintomas relacionados à SC foram relatados em condições dolorosas com o componente neuropático [16,17]. As pontuações do CSI foram relacionadas à intensidade da dor e à área da dor medida pelo Índice de Dor Generalizada (*Widespread Pain Index*) [18]. O comprometimento da modulação condicionada da dor (MCD) foi relatado em pacientes com dor musculoesquelética [19,20], dor crônica [21], e dor crônica generalizada nas costas e síndrome da fibromialgia [22]. Além disso, nosso grupo encontrou uma prevalência de 20% [23] e 25% [24] de MCD prejudicada em pacientes com dor musculoesquelética.

O questionário PainDETECT tem sido utilizado num grande número de condições musculoesqueléticas (dor lombar, artrite reumatóide, osteoartrite, dor oncológica e

[1] N.t.: várias ferramentas para a avaliação e manejo da dor estão livremente disponíveis para *download* no site pesquisaemdor.com.br, projeto do qual os autores deste artigo fazem parte.

espondilolistese lombar) [25]. O PainDETECT é uma das melhores opções para a triagem de sintomas do tipo neuropático (sensibilidade = 85% e especificidade = 95%) [26]. Além disso, a versão original em alemão do painDETECT apresentou consistência interna adequada (α de Cronbach = 0,76). Similarmente, a versão brasileira do painDETECT obteve consistência interna adequada para os nove itens (α de Cronbach de 0,74) e para os sete sintomas de dor sensorial (α de Cronbach de 0,83, 27). Por fim, o painDETECT é um instrumento de triagem simples e de baixo custo que pode fornecer maior clareza aos profissionais de saúde na avaliação e, consequentemente, na oferta de estratégias adequadas para o manejo de pacientes com dor musculoesquelética. Portanto, o presente estudo teve como objetivo comparar as características da dor de pacientes com dor musculoesquelética classificada como dor nociceptiva, indefinida e sintomas do tipo neuropático de acordo com o questionário painDETECT. Nós levantamos a hipótese de que pacientes com sintomas do tipo neuropático têm características clínicas desfavoráveis em comparação com pacientes com dor nociceptiva e indefinida.

Métodos

Desenho do estudo e considerações éticas

Foi utilizado um desenho de estudo transversal seguindo os requisitos do *STrengthening the Reporting of OBservational Studies in Epidemiology* (STROBE) [27]. Este estudo foi aprovado pelo Comitê de Ética em Pesquisa do Centro Universitário Augusto Motta (número: 03870618.5.0000.5235), de acordo com a Declaração de Helsinque para pesquisa em seres humanos. Todos os pacientes que preencheram os critérios de elegibilidade assinaram o termo de consentimento informado antes dos procedimentos do estudo.

Pacientes do estudo

Pacientes consecutivos com dor musculoesquelética (com idade igual ou superior a 18 anos) de dois ambulatórios de Fisioterapia (Hospital Universitário Gaffrée e Guinle e Centro Universitário Augusto Motta), duas clínicas particulares e um ambulatório de reabilitação multidisciplinar (Centro de Reabilitação Cabo Frio) no estado do Rio de Janeiro, Brasil, foram inscritos quando procuraram tratamento entre março e setembro de 2019. O estudo incluiu pacientes com dor aguda (duração da dor inferior a 3 meses) e dor crônica (duração da dor superior a 3 meses). A dor musculoesquelética foi definida como a dor percebida em uma região do corpo com origem muscular, ligamentar, óssea ou articular [2]. Foram excluídos do estudo pacientes que realizaram procedimento cirúrgico na coluna, gestantes, pacientes com diagnóstico reumatológico na fase inflamatória aguda, tumores, analfabetos ou que não conseguiam preencher os questionários autorrelatados.

Procedimentos

Os pacientes foram encaminhados para uma avaliação inicial composta da história clínica e do exame físico. A coleta dos dados sociodemográficos (idade, sexo, peso, altura, escolaridade e renda) e das características da dor (intensidade da dor, duração da dor, sinais e sintomas relacionados à SC e área da dor) foi realizada usando um questionário. Os sintomas do tipo neuropático foram medidos pelo questionário painDETECT. A intensidade da dor foi medida usando a Escala Numérica de Avaliação da Dor de 0 a 10 (ou seja, 0 significa sem dor e 10 significa a pior dor possível). A duração da dor foi registrada em meses. Sinais e sintomas relacionados à SC foram avaliados através do Inventário de Sensibilização Central (CSI). A dor generalizada foi avaliada por meio do Índice de Dor Generalizada. A Modulação Condicionada da Dor (MCD) foi avaliada pelo Cold Pressor Test[2]. Finalmente, a limitação funcional foi medida usando a Escala Funcional Específica do Paciente. O preenchimento de todos os questionários foi supervisionado por

[2] N.t.: Teste Pressório ao Frio. Foi mantida a denominação em inglês no texto por já ter se tornado usual no Brasil.

um examinador para esclarecimento no caso de incertezas e durou aproximadamente 10 minutos por participante. Após o preenchimento dos questionários, os pacientes foram encaminhados para a avaliação da MCD no mesmo dia.

Questionário painDETECT – O painDETECT é um questionário auto-administrado que engloba quatro domínios da seguinte forma: intensidade da dor (três questões), padrão de evolução da dor (quatro gráficos), áreas de dor e a presença de dor irradiada (desenho do mapa corporal), e itens descritores sensoriais de dor (sete questões). O primeiro domínio apresenta três questões referentes à intensidade da dor no momento, ao nível de dor mais forte (nas últimas 4 semanas) e ao nível de dor em média (nas últimas 4 semanas). A pontuação final é calculada por nove itens representados no últimos três domínios (padrão de evolução da dor, dor irradiada e gradação da dor). A pontuação do segundo domínio (padrão de evolução da dor) varia entre 0 e + 1, e as opções de resposta são: Dor persistente com pequenas flutuações = 0; Dor persistente com crises de dor = + 1; Crises de dor sem dor entre elas = + 1; e crises de dor com dor entre elas = + 1. O terceiro domínio (dor irradiada) tem a pergunta: "Sua dor irradia para outras regiões do seu corpo?". A resposta a esta questão é dicotômica (sim/não) e varia entre + 2 / 0. O quarto domínio (gradação da dor) possui sete questões com seis possíveis respostas para cada questão pontuando de 0 (nunca); 1 (quase imperceptível); 2 (muito pouco); 3 (moderada); 4 (forte); a 5 (muito forte). Uma pontuação final entre -1 e 38 pode ser obtida somando-se as pontuações dadas em cada domínio. O painDETECT é validado para um grande número de condições de dor neuropática [28-30]. Ele também foi validado para uso em condições de dor mista, como artrite reumatóide, osteoartrite, dor oncológica e espondilolistese lombar [25]. O ponto de corte para o questionário original indica que um componente neuropático é improvável nos escores ≤12, um componente neuropático é indefinido em pontuações entre 13 e 18, enquanto valores ≥19 indicam a probabilidade de um componente neuropático [25]. Para fins de triagem, consideramos pontuações ≤12 como dor nociceptiva, pontuações entre 13 e 18 como indefinidas, e escores ≥19 como dor neuropática. O questionário painDETECT foi adaptado transculturalmente ao contexto brasileiro [31].

Medidas de desfecho

A intensidade da dor foi medida durante a avaliação inicial usando a Escala Numérica de Avaliação da Dor de 0 (sem dor) a 10 (pior dor possível). Os participantes foram orientados a avaliar a sua intensidade de dor no momento da avaliação inicial. A duração da dor foi registrada em meses, e os pacientes foram classificados com tendo dor musculoesquelética crônica se tivessem dor por mais de 3 meses, de acordo com a Associação Internacional para o Estudo da Dor (*International Association for the Study of Pain* - IASP) [32].

Sinais e sintomas relacionados à SC – O Inventário de Sensibilização Central (CSI) identificou pacientes cujos sintomas apresentados podem estar relacionados à sensibilização central. O CSI é um instrumento desenvolvido para identificar sinais e sintomas relacionados à SC [33]. A Parte A avalia 25 sintomas relacionados à saúde comumente observados em pacientes com síndrome de sensibilidade central e é pontuado numa escala Likert de 5 pontos que vai de 0 (nunca) a 4 (sempre), com um total de 100 pontos. Pontuações mais altas representam um aumento na gravidade dos sintomas. A parte B não é pontuada e engloba dez diagnósticos prévios de um indivíduo, incluindo sete síndromes de sensibilidade central e três distúrbios relacionados à síndrome de sensibilização central. O ponto de corte ideal foi estabelecido em 40/100 em pacientes com síndrome de sensibilidade central [34, 35]. Além disso, a gravidade dos sinais e sintomas relacionados à SC tem sido classificada em subclínica (0-29), leve (30–39), moderada (40-49), grave (50-59) e extrema (60-100), onde pontuações mais altas indicam um aumento na gravidade dos sintomas. A versão

brasileira do CSI demonstrou fortes propriedades psicométricas [36].

Área de dor – O Índice de Dor Generalizada foi usado para diagnosticar a dor generalizada. O Índice de Dor Generalizada é composto por uma lista de 19 áreas do corpo. Cintura escapular, braço, antebraço, quadril, coxa, perna e mandíbula são todas consideradas à esquerda e à direita. As áreas do peito, abdômen, parte superior das costas, parte inferior das costas e pescoço também compõe o Índice de Dor Generalizada [37]. O paciente é orientado a marcar as áreas referentes à dor durante a semana passada. Cada área marcada equivale a um ponto, e a pontuação final varia entre 0 e 19 pontos. As diretrizes atuais recomendam o uso do Índice de Dor Generalizada para a identificação de dor generalizada [37, 38]. Dor generalizada é definida como a presença de dor em pelo menos 4 de 5 regiões (sendo as regiões os 4 quadrantes e a região axial). As cinco áreas são divididas em Região 1 – região superior esquerda, mandíbula, cintura escapular, braço e antebraço (esquerdos); Região 2 – região superior direita, mandíbula, cintura escapular, braço e antebraço (direitos); Região 3 - região inferior esquerda, quadril, coxa e perna (esquerdas); Região 4 – região inferior direita, quadril, coxa e perna (direitas) e Região 5 – região axial, pescoço, parte superior das costas, parte inferior das costas, tórax e abdômen. Dor mandibular,no tórax e no abdômen não estão incluídas na definição de dor generalizada [37]. O Índice de Dor Generalizada demonstrou propriedades psicométricas adequadas em jovens [39].

Modulação Condicionada da Dor (MCD) - O Cold Pressor Test é um teste psicofísico usado para avaliar a MCD, onde a dor fria é o estímulo condicionante e o limiar de dor à pressão é o estímulo de teste. O Cold Pressor Test é um método apropriado para avaliar o sistema inibitório nociceptivo descendente [40] e o mais frequentemente usado para a avaliação da modulação condicionada de dor [41]. O estímulo condicionante foi a imersão da mão do participante em um balde com água fria em temperatura controlada (1 °C – 4 °C) monitorada por um termômetro (modelo 5130, *Incoterm*), por até 1 minuto. O participante foi orientado a permanecer com a mão imersa na água sem fazer contrações musculares ou alterações em posição. A retirada da mão da água foi permitida quando o paciente não podia mais tolerar o estímulo doloroso. A temperatura do ambiente, umidade, iluminação e ruído foram mantidos constantes durante todo o procedimento. O limiar de dor à pressão foi realizado antes e após 1 minuto do Cold Pressor Test, usando um algômetro de pressão digital (modelo Force Ten FDX, *Wagner Instruments*, Greenwich, EUA). A parte distal do antebraço dorsal e do músculo tibial anterior, que não haviam sido imersos em água, foram escolhidos para serem avaliados devido à falta de relação com as queixas musculoesqueléticas dos participantes. Os dois locais foram avaliados na mesma ordem para todos os participantes. O funcionamento do algômetro de pressão e a medição do limiar de dor à pressão foram explicados aos pacientes antes da avaliação. Além disso, um procedimento de familiarização foi realizado com o algômetro de pressão aplicando-se pressão no antebraço dominante para garantir que o teste tinha sido compreendido. A força foi gradualmente aumentada (1 kg-força/s) até que a sensação de pressão do sujeito primário fosse alterada para dor. O limiar de dor à pressão foi registrado em quilogramas-força (Kgf) quando o paciente deu o comando verbal "dor". A classificação da eficiência da MCD foi baseada na seguinte estratégia: evidência de modulação da dor prejudicada em dois locais. Apenas pacientes com ineficiência do MCD em ambas as localizações (músculo tibial anterior e parte distal do antebraço dorsal) foram classificados como apresentando modulação da dor prejudicada. Locais nos membros superiores e inferiores foram utilizados para evitar a inclusão dos pacientes com sensibilização periférica, conforme recomendações para a modulação condicionada da dor [42]. Além disso, a eficiência da MCD foi avaliada calculando a diferença entre os valores do limiar de dor à pressão no Cold

Pressor Test (diferenças entre o valor final e inicial). Valores negativos representaram uma ineficiência da MCD, e valores nulos ou positivos foram considerados uma resposta típica da MCD.

Limitação funcional - A Escala Funcional Específica do Paciente é uma medida auto-relatada usada para avaliar a alteração funcional em pacientes com distúrbios musculoesqueléticos. Os pacientes devem identificar até cinco atividades importantes que eles são incapazes de realizar ou estão tendo dificuldades como resultado de seu problema. Então, classificam o nível atual de dificuldade associado a cada atividade numa escala de 11 pontos. A Escala Funcional Específica do Paciente tem fácil aplicabilidade e pode ser usada como medida de desfecho clínico [43].

Análise estatística

As variáveis demográficas e clínicas da população do estudo foram resumidas como média (desvio padrão) para variáveis contínuas. As variáveis categóricas são apresentadas em frequência absoluta (percentual) da amostra. Para variáveis contínuas, a distribuição normal dos desfechos do estudo foi verificada pelo teste de Shapiro-Wilk. Foi usada a análise de variância unidirecional independente (ANOVA) para testar as diferenças entre os grupos (dor nociceptiva, dor incerta ou sintomas do tipo neuropático) para as medidas de desfecho com variáveis contínuas (ou seja, intensidade da dor, duração da dor, sinais e sintomas relacionados à SC, dor generalizada e limitação funcional), e o teste qui-quadrado de Pearson (X^2) verificou diferenças entre os grupos na eficiência da modulação condicionada da dor. Os testes post-hoc de Tukey foram usados para comparações múltiplas de médias. Um nível de significância inferior a 5% (P < 0,05) foi considerado para todas as análises. A análise estatística foi realizada usando JASP versão 0.10.2.0 e Prism para Macintosh, Versão 8 (*GraphPad Software Inc.*, San Diego, CA).

Tabela 1 Características dos participantes do estudo (n = 308)

Características	Dor nociceptiva *n* = 173	Indefinida *n* = 69	Sintomas do tipo neuropático (*n*=66)	Valor *p*
Sexo, n (%), feminino	120 (69,36%)	47 (68,11%)	53 (80,30%)	0,194
Idade, média (DP)	52,26 (15,99)	51,43 (14,72)	52,92 (12,41)	0,846
Peso (kg), média (DP)	72,83 (16,99)	75,17 (14,08)	72,54 (13,64)	0,546
Altura (m), média (DP)	1,64 (0,11)	1,65 (0,11)	1,60 (0,16)	0,104
Índice de Massa Corporal (kg/m^2), média (DP)	26,55 (6,60)	28,01 (4,76)	30,86 (25,50)	0,098
Horas de trabalho (semanais), média (DP)	41,50 (14,75)	45,81 (15,48)	43,60 (17,24)	0,454
Plano de saúde (Sim), n (%)	46 (26,59%)	11 (15,94%)	14 (21,21%)	0,170
Atividade física (Sim), n (%)	95 (54,91%)	31 (44,92%)	33 (50,00%)	0,425
Pontuação final painDETECT, média (DP)	6,23 (3,47)c	15,14 (1,49)	23,54 (3,77)a,b	<001
Intensidade da dor, média (DP)	5,26 (2,51)	5,88 (2,14)	7,42 (2,09)	<001
Duração da dor (meses), média (DP)	62,33 (105,78)	59,49 (85,99)	85,58 (100,01)	0,231
CSI, média (DP)	27,75 (14,26)c	38,53 (14,92)	49,43 (15,94)a,b	<001
Índice de Dor Generalizada, média (DP)	3,84 (3,36)c	6,02 (4,26)	8,24 (5,58)	<001
Teste Pressório ao Frio, sim, n (%)	32 (18,49%)	15 (21,73%)	13 (19,69%)	0,847
Escala FuncionalEspecífica do Paciente, média (DP)	6,77 (2,05)	7,19 (1,81)	8,04 (1,87)	<001

Nota: Os dados são apresentados como média (DP) para variáveis contínuas e como contagem de frequência (%) para variáveis categóricas. Diferenças significativas entre os grupos foram testadas usando o teste t não pareado para variáveis contínuas ou o teste qui-quadrado para variáveis categóricas. **a** Representa uma diferença significativa entre o grupo de sintomas tipo neuropáticos e o grupo de dor nociceptiva; **b** Representa uma diferença significativa entre o grupo de sintomas do tipo neuropático e o grupo indefinido; **c** Representa uma diferença significativa entre o grupo de dor nociceptiva e o grupo indefinido;. Abreviaturas: CSI, Inventário de Sensibilização Central; DP, Desvio-Padrão.

Resultados

Características dos participantes

Um total de 308 pacientes com dor musculoesquelética, com média de idade de 52,21 (±15,01) anos e 220 (71,42%) mulheres foi incluído neste estudo. Cento e setenta e três (56,16%) participantes foram classificados como apresentando dor nociceptiva, 69 (22,40%) participantes foram classificados como dor indefinida e 66 (21,42%) como sintomas do tipo neuropático. A dor generalizada foi descrita por 33 (19,07%) pacientes com dor nociceptiva, 31 (44,92%) pacientes classificados como dor indefinida, e por 33 (50,00%) pacientes com sintomas do tipo neuropático. Além disso, 60 (19,48%) participantes foram classificados como apresentando MCD comprometida. Todos os participantes preencheram os questionários e completaram o Cold Pressor Test sem eventos adversos. Dessa forma, não houve dados incompletos para os desfechos do estudo. As características da amostra do estudo são mostradas na Tabela 1.

Comparação das características da dor, sinais e sintomas relacionados à SC, dor generalizada, limitação funcional e modulação condicionada da dor

Uma ANOVA mostrou diferenças para a intensidade da dor [F (2,305) = 20,097; p < 0,001], sinais e sintomas relacionados à Sensibilização Central [F (2,305) = 54,186; p < 0,001], área da dor [F (2,305) = 28,525; p < 0,001] e limitação funcional [F (2,256) = 8,061; p < 0,001]. A MCD foi similarmente prejudicada entre os três grupos (X^2 = 0,333, p = 0,847).

Discussão

Este estudo comparou as características da dor de pacientes com dor musculoesquelética classificada como dor nociceptiva, dor indefinida e sintomas do tipo neuropático de acordo com o questionário painDETECT. Nossa amostra demonstrou características demográficas e clínicas semelhantes entre os grupos, mas fenótipos diferentes de dor. Pacientes com sintomas do tipo neuropático tiveram intensidade de dor mais pronunciada, níveis mais elevados de sinais e sintomas relacionados à SC e apresentaram mais dor generalizada do que os pacientes classificados como tendo dor nociceptiva, confirmando nossa hipótese. A MCD demonstrou ser semelhante entre os três grupos. Além disso, a funcionalidade foi mais restrita em pacientes com sintomas do tipo neuropático do que em pacientes nos grupos de dor nociceptiva e indefinida.

Os achados presentes revelaram que o painDETECT foi capaz de identificar diferentes fenótipos de dor musculoesquelética. Identificar esses fenótipos pode ter relevância para a prática clínica e auxiliar no desenvolvimento de intervenções adequadas para o tratamento de pacientes com distúrbios musculoesqueléticos [5]. Além disso, a avaliação de fenótipos foi realizada em estudos prévios com pacientes com dor musculoesquelética. Pacientes com osteoartrite do joelho classificada como sintomas do tipo neuropático no painDETECT apresentam maior dor, dor generalizada e função física comprometida em comparação com outros grupos [44]. Os autores concluíram que o reconhecimento de pacientes de osteoartrite de joelho com este fenótipo pode oferecer abordagens direcionadas e eficazes [44]. Ademais, pacientes de dor lombar crônica com sintomas do tipo neuropático relataram dor mais intensa, pior saúde física e mental, exibiram maior incapacidade relacionada à dor nas costas, sinais de depressão e sofrimento psicológico quando comparados a pacientes de dor lombar crônica classificados como tendo dor nociceptiva [12]. Em última análise, o painDETECT detectou perfis clínicos distintos para pacientes com dor lombar crônica.

Nossos achados revelaram que os pacientes classificados como apresentando sintomas do tipo neuropático tiveram um número maior de

áreas de dor e maiores níveis de sintomas de sensibilização central do que pacientes com classificação nociceptiva ou indefinida. Anormalidades sensoriais bilaterais foram encontradas em pacientes com dor neuropática unilateral [45], e pacientes com neuropatias periféricas tiveram diferenças sensoriais mínimas entre a área afetada e a não afetada [46]. Pacientes com dor no joelho do tipo neuropática mostraram associação significativa com dor generalizada em comparação com outros pacientes [47]. Da mesma forma, pacientes com síndrome do túnel do carpo unilateral apresentaram hiperalgesia térmica bilateral, sustentando o papel de mecanismos de dor de sensibilização generalizada [48]. Estudos anteriores relacionam a dor generalizada e a sensibilização central [17, 49-52], e há evidência clínica de que a sensibilização central está presente em pacientes com dor neuropática [19]. Além disso, a sensibilização generalizada foi descrita em muitas condições musculoesqueléticas por exemplo, enxaqueca e cefaléia do tipo tensional crônica [53], osteoartrite dolorosa do joelho [54] e epicondilite unilateral [55]). Portanto, nossos achados destacam a relação entre dor generalizada e sintomas de sensibilização central em pacientes com sintomas do tipo neuropático.

Várias abordagens estão disponíveis para avaliar a sensibilização central. O CSI é uma ferramenta de previsão clinicamente útil, independentemente de pacientes com distúrbios musculoesqueléticos [56]. Outra estratégia para avaliar a sensibilização central é a MCD através do Cold Pressor Test, que avalia o sistema inibitório nociceptivo descendente. Nossos achados revelaram que os pacientes classificados com sintomas do tipo neuropático apresentam escores mais altos no CSI. Este resultado é consistente com estudos anteriores que mostram que a sensibilização central se manifesta mais em condições dolorosas com o componente neuropático [16, 17]. No entanto, o presente estudo mostrou que 19% dos pacientes classificados como sintomas do tipo neuropático apresentaram um comprometimento da modulação condicionada da dor (MCD), revelando que escores mais altos no CSI não têm relação com uma MCD prejudicada. Além disso, pontuações do CSI não estiveram associadas com a eficiência da MCD [18, 57], e o CSI teve aplicabilidade limitada para detectar o déficit da MCD em pacientes com dor musculoesquelética [58]. As propriedades adequadas de medição do CSI podem estar relacionadas a um subgrupo particular de pacientes com aspectos psicossociais [58], considerando que os escores do CSI estão mais associados a ansiedade e depressão do que a medidas psicofísicas de sensibilização central [57, 59].

Reconhecemos os pontos fortes e as limitações do presente estudo. Em primeiro lugar, este é o primeiro estudo a comparar as características de dor de pacientes com sintomas nociceptivos, indefinidos e do tipo neuropático de forma conjunta. Segundo, o painDETECT é uma ferramenta de triagem bem reconhecida para a identificação de sintomas do tipo neuropático [60]. Finalmente, o grande tamanho amostral pode ser considerado como um ponto forte deste estudo. Em relação às limitações do estudo, em primeiro lugar há a falta de um diagnóstico de condição de saúde, o que pode afetar os achados em condições específicas. Em segundo lugar, o Cold Pressor Test não é o padrão-ouro para o diagnóstico de comprometimento da MCD. No entanto, o Cold Pressor Test é o método mais frequentemente usado para avaliação da MCD [41]. Por fim, o presente estudo tem um desenho transversal, o que limita a generalização dos achados. No entanto, nós adotamos um desenho multicêntrico e implementamos vários métodos para minimizar o risco de viés, seguindo as diretrizes correntes para estudos deste tipo.

Nosso estudo fornece novas ideias para a implementação do painDETECT em seu uso clínico e em estudos posteriores. O painDETECT é uma ferramenta de triagem simples e de baixo custo para avaliar e identificar sintomas do tipo neuropático, e deve ser implementado para avaliar fenótipos de dor em pacientes com dor musculoesquelética heterogênea. A identificação das características de dor em pacientes com dor musculoesquelética

contribui para um tratamento bem adaptado. Assim, os profissionais de saúde são incentivados a incorporar, em sua prática, estratégias para o manejo de pacientes com dor musculoesquelética de acordo com sua predominância de dor (ou seja, nociceptiva ou neuropática). Clínicos devem estar cientes das características de dor mais graves dos pacientes com um componente neuropático. Estudos futuros em diferentes populações e cenários são necessários para comparar as características de dor musculoesquelética de acordo com sua predominância.

Conclusão

O painDETECT identifica fenótipos diferentes de dor musculoesquelética. Pacientes com sintomas do tipo neuropático revelaram características de dor desfavoráveis em comparação com seus pares, incluindo a intensidade da dor, sinais e sintomas relacionados à SC, dor generalizada e limitação funcional.

Agradecimentos
Não aplicável.

Consentimento informado
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A pesquisa relacionada ao uso humano está em conformidade com todos os regulamentos nacionais relevantes, políticas institucionais, e foi realizada de acordo com os princípios da Declaração de Helsinque, tendo sido aprovada pelo comitê de revisão institucional dos autores.
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O questionário painDETECT identifica a modulação condicionada de dor prejudicada em pessoas com dor musculoesquelética? - Um estudo de acurácia diagnóstica

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Resumo

Introdução: Pessoas com sintomas do tipo neuropático apresentaram características de dor mais desfavoráveis do que pessoas com sintomas nociceptivos. Além disso, a modulação condicionada da dor deficiente é comum em pessoas com sintomas do tipo neuropático. O questionário PainDETECT tem sido usado para avaliar o sinal e os sintomas de sensibilização central. No entanto, ainda não se sabe se o questionário PainDETECT pode identificar o comprometimento da modulação condicionada da dor. Portanto, o objetivo do presente estudo foi avaliar a acurácia diagnóstica do questionário painDETECT na detecção do comprometimento da modulação condicionada da dor em pessoas com dor musculoesquelética.

Métodos: Realizamos uma acurácia diagnóstica comparando o questionário painDETECT (método índice) com o *Cold Pressor Test* (CPT), o teste psicofísico usado para avaliar a modulação condicionada da dor (padrão de referência). Determinamos a acurácia diagnóstica calculando a sensibilidade, a especificidade, os valores preditivos e as razões de probabilidade.

Resultados: Inscrevemos, retrospectivamente, 308 pessoas com dor musculoesquelética em departamentos ambulatoriais. A maioria dos participantes era do sexo feminino (n 20 = 220, 71,4%) e tinha uma idade média de 52,2 (± 15,0) anos. Cento e setenta e três (56,1%) participantes foram classificados como dor nociceptiva, 69 (22,4%) como incerto e 66 (21,4%) como sintomas do tipo neuropático. De acordo com o *Cold Pressor Test*, 60 (19,4%) participantes apresentaram comprome-

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timento da modulação condicionada da dor. O ponto de corte de 12 do questionário painDETECT mostrou valores de acurácia diagnóstica abaixo de 70% em comparação com o *cold pressor test*, exceto por um valor preditivo negativo [76,9 Intervalo de Confiança (IC) de 95% 71,7 a 81,5]. O ponto de corte 19 mostrou alta especificidade (78,6%, IC 95% 73,0 a 83,5), alto valor preditivo negativo (80,5 IC 95% 78,1 a 82,7) e acurácia de 67,5% em comparação com o *cold pressor test*.

Conclusão: O questionário painDETECT parece ser valioso para descartar pessoas com dor musculoesquelética e comprometimento da modulação condicionada da dor.

Palavras-chave: Dor musculoesquelética, Dor neuropática, Mecanismos de dor, Sensibilização do sistema nervoso central, Controle inibitório nocivo difuso

O que já se sabe sobre esse tópico?

- O painDETECT é uma ferramenta de triagem para identificar sintomas do tipo neuropático.
- Pessoas com sintomas do tipo neuropático têm comprometimento da modulação da dor.

O que este estudo acrescenta?

- O ponto de corte de 19 apresentou alta especificidade e valor preditivo negativo em comparação com o *cold pressor test*.
- Nossos dados sugerem que o questionário painDETECT é um instrumento valioso para descartar pessoas com dor musculoesquelética e comprometimento da modulação condicionada da dor.

Contexto

A dor neuropática leva a resultados desfavoráveis e continua sendo um grande desafio clínico. Pessoas com sintomas do tipo neuropático apresentaram características de dor desfavoráveis (por exemplo, intensidade da dor e limitação funcional) em comparação com suas contrapartes [1]. Estudos anteriores mostraram que a dor neuropática interfere em vários aspectos da vida de um indivíduo, como a má qualidade do sono [2], a disfunção física [3] e uma grande carga psicossocial [4]. Além disso, há uma alta prevalência de depressão entre as pessoas com dor neuropática, o que prejudica a qualidade de vida [5]. Existem ferramentas de triagem capazes de identificar os principais sintomas do tipo neuropático. O questionário painDETECT é uma ferramenta de triagem confiável, simples e validada para identificar sintomas do tipo neuropático em pessoas com dor lombar crônica [6]. O questionário painDETECT foi validado para várias doenças, incluindo artrite reumatoide, osteoartrite, fibromialgia, dor do câncer e espondilolistese lombar [7]. Além disso, comparado a outros instrumentos disponíveis, o questionário painDETECT é uma das melhores opções para triagem de sintomas do tipo neuropático (apresentando 85% de sensibilidade, 80% de especificidade e 83% de acurácia preditiva positiva) [8]. Assim, o uso do questionário painDETECT é popular entre pesquisadores e clínicos para identificar sintomas do tipo neuropático em pessoas com dor musculoesquelética.

A dor neuropática está envolvida com a sensi-bilização central (SC) e periférica. Há vários instrumentos disponíveis para identificar as características clínicas da SC na população musculoesquelética [9]. O *cold pressor test* é um dos paradigmas mais adequados de modulação condicionada da dor para avaliar as vias modulatórias nociceptivas descendentes [10].

Pessoas com sintomas do tipo neuropático têm comprometimento da modulação da dor, o que é considerado indicativo de sinais e sintomas relacionados à sensibilização central [11, 12]. Por exemplo, a síndrome do túnel do carpo [13], a neuropatia diabética dolorosa [14], a neuropatia periférica dolorosa [15] e a síndrome da dor regional complexa [16] têm uma modulação condicionada da dor prejudicada. Da mesma forma, pessoas com dor presumivelmente nociceptiva demonstraram sinais e sintomas relacionados a SC. Lluch et al. mostraram que 28 a 34% das pessoas com dor no joelho causada por osteoartrite tinham sinais e sintomas relacionados a SC, considerando diferentes aspectos dos sinais e sintomas relacionados a SC (ou seja, manifestações clínicas da SC, resultados de testes sensoriais quantitativos, inibição nociceptiva endógena disfuncional e neuroimagem) [17]. Além disso, a interação entre a osteoartrite do joelho e a SC aumentou o desconforto noturno e a incapacidade [18]. Abordagens fisioterapêuticas (por exemplo, educação, exercícios, terapia manual e estimulação elétrica neural transcutânea) podem ter como alvo fenótipos específicos de dor e individualizar o atendimento [19]. Portanto, detectar o comprometimento da modulação condicionada da dor em pessoas que apresentam dor musculoesquelética (como, dor nociceptiva e sintomas do tipo neuropático) pode ajudar os clínicos a oferecer estratégias terapêuticas adequadas para esses grupos.

O uso do questionário painDETECT na avaliação de sinais e sintomas relacionados a SC tem sido defendido. O PainDETECT foi concebido como uma ferramenta de triagem, mas também pode funcionar como uma medida das características que apontam para o aumento do processamento central da dor [20]. Gwylim et al. revelaram que pessoas com pontuações mais altas no questionário painDETECT tinham mais sinais de SC [21]. Da mesma forma, o questionário painDETECT modificado pode ajudar a identificar a SC em adultos com osteoartrite de joelho, uma vez que pontuações mais altas do questionário painDETECT modificado (> 12) tinham 5,6 vezes mais probabilidade de apresentar sinais e sintomas relacionados a SC [22]. É importante observar que o estudo anterior selecionou pessoas com osteoartrite de joelho usando o painDETECT modificado, que tem como alvo os sintomas "no ou ao redor" de cada joelho, em vez de sua "área principal de dor", dor que se espalha para cima ou para baixo a partir do joelho e uma figura com gênero neutro [22]. Não está claro se os resultados do questionário painDETECT podem detectar pessoas com comprometimento da modulação da dor. Portanto, o objetivo do presente estudo foi avaliar a acurácia diagnóstica do questionário painDETECT na detecção do comprometimento da modulação condicionada da dor em pessoas com dor musculoesquelética.

Métodos

Desenho de estudo e considerações éticas

Realizamos e relatamos um estudo de acurácia diagnóstica seguindo as diretrizes do *Standards for Reporting of Diagnostic Accuracy Studies* (STARD) [23] (Arquivo adicional 1). O Comitê de Ética em Pesquisa do Instituto Federal do Rio de Janeiro aprovou este estudo (número: 02228818.0.3001.5258) de acordo com a Declaração de Helsinque para pesquisa em seres humanos. Todas as pessoas com dor musculoesquelética que atenderam aos critérios de elegibilidade assinaram o termo de consentimento livre e esclarecido antes de se submeterem aos procedimentos do estudo.

População do estudo

Recrutamos retrospectivamente pessoas com dor musculoesquelética em dois departamentos públicos de fisioterapia (Hospital Universitário Gaffrée e Guinle e Centro de Reabilitação de Cabo Frio) e três departamentos privados de fisioterapia (Centro Universitário Augusto Motta, Clínica de Fisioterapia Saúde Clin e Clínica de Fisioterapia Fisiofit) nos estados do Rio de Janeiro e Minas Gerais, Brasil, entre março e setembro de 2019. Nos departamentos públicos de fisioterapia, ortopedistas, clínicos gerais ou outros profissionais de saúde frequentemente encaminharam pessoas com dor musculoesquelética. Em todos os departamentos de fisioterapia privados, as pessoas relataram ter procurado atendimento para sua condição musculoesquelética principalmente devido à dor.

O estudo envolveu pessoas com dor aguda (menos de três meses) e dor crônica (duração da dor superior a três meses). Definimos dor musculoesquelética como dor originária de músculos, ligamentos, ossos ou articulações em uma região específica do corpo [24]. Excluímos pessoas que haviam sido submetidas a cirurgia na coluna, mulheres grávidas, pessoas na fase inflamatória aguda de diagnósticos reumatológicos, pessoas com tumores, analfabetos ou pessoas incapazes de preencher os questionários autorrelatados.

Procedimentos

A avaliação incluiu o histórico clínico, o exame físico e o cold pressor test realizados no mesmo dia para pessoas com dor musculoesquelética. Coletamos informações sociodemográficas e clínicas usando um instrumento que incluía dados demográficos (idade, sexo, peso, altura, nível de escolaridade e renda), bem como características da dor musculoesquelética (intensidade e duração da dor). Medimos a intensidade da dor usando a Escala Numérica de Dor, que varia de 0 a 10 (0 representa ausência de dor e 10 ilustra a pior dor possível). Essa escala é comumente usada em estudos de dor musculoesquelética e tem demonstrado bons níveis de reprodutibilidade [25]. A duração da dor foi registrada em meses, sendo a dor crônica definida como aquela com duração superior a três meses e a dor aguda com duração inferior a três meses [26]. Os sintomas do tipo neuropático foram medidos usando o questionário painDETECT, com a versão brasileira se mostrando útil na identificação desses sintomas [27]. O *cold pressor test* avaliou a Modulação Condicionada de Dor (MCD), que avalia o sistema inibitório nociceptivo descendente [28, 29]. Um examinador supervisionou o preenchimento de todos os questionários, fornecendo esclarecimentos quando necessário, e o processo levou aproximadamente 10 minutos por pessoa com dor musculoesquelética. Após o preenchimento dos questionários, os pacientes com dor musculoesquelética foram encaminhados para avaliação da MCD.

Método de índice

O questionário PainDETECT é uma ferramenta autoadministrada usada para avaliar sintomas do tipo neuropático. Ele é composto por quatro domínios com os seguintes componentes: intensidade da dor (três perguntas), padrão do curso da dor (quatro gráficos), áreas de dor e presença de dor irradiada (desenho do gráfico corporal) e itens descritores sensoriais da dor (sete perguntas). O primeiro domínio consiste em três perguntas que avaliam a intensidade da dor, incluindo os níveis mais intensos e de média de dor nas últimas quatro semanas. A pontuação final é calculada com base em uma representação de nove itens dos três últimos domínios (padrão de curso da dor, dor irradiada

e gradação da dor). O segundo domínio (padrão de curso da dor) tem opções de resposta de Dor persistente com pequenas flutuações = 0, Dor persistente com ataques de dor = -1, Ataques de dor sem dor entre eles = + 1 e Ataques de dor com dor entre eles = + 1. A pontuação para esse domínio varia entre 0 e + 1. O terceiro domínio (dor irradiada) inclui uma pergunta dicotômica: "*Sua dor irradia para outras regiões do corpo?*" com opções de resposta de sim ou não, correspondendo a pontuações de + 2 ou 0, respectivamente. O quarto domínio (gradação da dor) é composto por sete perguntas, cada uma com seis respostas possíveis, pontuadas de 0 (nunca) a 5 (fortemente). As pontuações dadas em cada domínio são somadas para se obter uma pontuação final que varia de -1 a 38. O questionário PainDETECT foi validado para condições de dor neuropática [30-32] e também foi validado para condições mistas de dor, como artrite reumatoide, osteoartrite, dor de câncer e espondilolistese lombar [33]. Os pontos de corte do questionário original indicam que escores ≤ 12 sugerem que um componente neuropático é improvável, escores entre 13 e 18 mostram um componente neuropático incerto, enquanto escores ≥ 19 sugerem um provável componente neuropático [33]. Para fins de triagem, consideramos escores ≤ 12 indicativos de dor nociceptiva, escores entre 13 e 18 como incertos e escores ≥ 19 indicativos de sintomas do tipo neuropático. O questionário PainDETECT foi adaptado culturalmente para o contexto brasileiro [27].

Método de referência

A medida psicofísica do sistema inibitório nociceptivo descendente

Usamos o *cold pressor test* como uma medida psicofísica para avaliar o sistema inibitório nociceptivo descendente [34] e avaliar a modulação condicionada da dor [35]. Nesse teste, o estímulo condicionante foi a imersão das mãos das pessoas em um balde de água fria com temperatura controlada (1ºC - 4ºC) por até um minuto. Monitoramos a temperatura da água usando um termômetro (mod. 5130, *Incoterm*). As pessoas com dor musculoesquelética foram instruídas a manter as mãos imersas na água sem fazer contrações musculares ou mudar de posição. Elas podiam retirar a mão da água quando não conseguissem mais tolerar o estímulo doloroso. Mantivemos a temperatura ambiente, a umidade, a iluminação e o ruído constantes durante todo o procedimento.

Limiar de dor por pressão

Usamos um algômetro de pressão digital (modelo *Force Ten FDX*, Wagner Instruments, Greenwich, EUA) para medir o limiar da dor. Realizamos a avaliação do limiar de dor por pressão um minuto antes e após o cold pressor test. A avaliação foi realizada na parte distal do dorso do antebraço e no músculo tibial anterior, que não haviam sido imersos em água e não estavam relacionados às queixas musculoesqueléticas das pessoas. A avaliação foi feita na mesma ordem para todas as pessoas com dor musculoesquelética. Antes da avaliação, explicamos o funcionamento do algômetro de pressão e como o limiar de dor por pressão seria medido. Também realizamos um procedimento de familiarização aplicando pressão no antebraço dominante, garantindo que as pessoas com dor musculoesquelética entendessem o teste. A força no algômetro foi aumentada gradualmente (1 kg-força/s) até que o sujeito primário sentisse uma mudança de pressão para dor. O limiar de dor por pressão foi registrado em quilogramas-força (Kgf) quando as pessoas com dor musculoesquelética indicaram verbalmente que estavam sentindo dor. Classificamos a eficiência da modulação condicionada da dor com base na seguinte

estratégia: evidência de comprometimento da modulação da dor em ambos os locais avaliados. Somente as pessoas com dor musculoesquelética que apresentaram comprometimento da modulação condicionada da dor tanto no músculo tibial anterior quanto na parte distal do dorso do antebraço foram classificadas como tendo comprometimento da modulação condicionada da dor. O uso de locais nos membros superiores e inferiores teve como objetivo evitar a inclusão de pessoas com sensibilização periférica, seguindo as recomendações para a modulação condicionada da dor [36]. A eficiência da modulação condicionada da dor foi avaliada calculando-se a diferença entre os valores de limiar de dor por pressão obtidos durante o *cold pressor test* (a diferença entre os valores final e inicial). Os valores negativos indicaram uma ineficiência da modulação condicionada da dor, enquanto os valores nulos ou positivos foram considerados uma resposta típica da modulação condicionada da dor.

Análise estatística

As variáveis demográficas e clínicas da população do estudo foram apresentadas como a média e o desvio padrão para variáveis contínuas. As variáveis categóricas foram apresentadas como valores absolutos e frequências. A análise de variância (ANOVA) independente e unidirecional foi usada para testar as diferenças intragrupo e intergrupos (dor nociceptiva, incertos, ou do tipo neuropático) para as medidas de resultado com variáveis contínuas (ou seja, valores de limiar de dor por pressão para a região dorsal do antebraço e tibial anterior dos participantes). A acurácia do diagnóstico do questionário painDETECT (método de avaliação) foi comparada com a medida psicofísica do sistema inibitório nociceptivo descendente (padrão de referência). Calculamos a sensibilidade, a especificidade, a razão de verossimilhança, a razão de verossimilhança positiva, a razão de verossimilhança negativa, a prevalência da doença, o valor preditivo positivo, o valor preditivo negativo e a acurácia com os correspondentes intervalos de confiança (ICs) binomiais de 95% exatos para dois pontos de corte predefinidos (12 e 19). Para os testes de acurácia diagnóstica (ou seja, sensibilidade, especificidade, valores preditivos e acurácia), os valores < 50% foram interpretados como baixos, 50% a 70% como moderados e > 70% a 100% como altos. Um nível de significância de menos de 5% ($p < 0,05$) foi considerado em todas as análises. A análise estatística foi realizada pelo Jeffreys's Amazing Statistics Program (JASP), versão 0.16.3, e pelo *Prism* para Macintosh, versão 8 (*GraphPad Software Inc.*, San Diego, CA).

Cálculo do tamanho da amostra

O cálculo da amostra foi baseado nos valores obtidos no estudo de Gervais-Hupé et al. [37]. Os autores observaram uma sensibilidade de 61,5% e uma especificidade de 77,6% na identificação da modulação condicionada da dor prejudicada usando o ponto de corte de 12 no questionário painDETECT em pessoas com osteoartrite de joelho. A estimativa foi calculada considerando a prevalência de sensibilização central de 21,43% em pessoas com dor musculoesquelética [38], o valor alfa de 5% e a acurácia da estimativa de 12%. Portanto, foi necessário incluir 295 pessoas com dor musculoesquelética.

Resultados

Características dos participantes

Um total de 308 pessoas com dor musculoesquelética foi registrado. A maioria dos participantes era do sexo feminino (n 20 = 220, 71,4%), tinha uma idade média de 52,2 (± 15,0)

anos e uma média de intensidade de dor moderada (Tabela 1). Duzentos e sessenta e seis (86,3%) participantes tinham dor crônica e 42 (13,6%) tinham dor aguda. No geral, 43 (13,9%) pessoas com dor musculoesquelética relataram um diagnóstico prévio de fibromialgia, 48 (15,5%) pessoas com dor musculoesquelética descreveram enxaqueca, 80 (25,9%) pessoas com dor musculoesquelética tinham ansiedade e 73 (23,7%) pessoas com dor musculoesquelética tinham um histórico anterior de transtorno depressivo. A dor lombar (n = 166, 53,8%) foi a principal queixa, seguida pela parte superior das costas (n = 136, 44,1%), ombro direito (n = 131, 42,5%), pescoço (n = 123, 39,9%) e ombro esquerdo (n = 116, 37,9%).

Tabela 1 Características das pessoas do estudo com dor musculoesquelética (n = 308)

Características	Valores (n = 308)
Sexo (feminino), n (%)	220 (71.4%)
Idade (anos), média (DP)	52.2 (± 15.0)
Peso (kg), média (DP)	73.3 (± 16.6)
Altura (metros), média (DP)	1.6 (± 0.1)
Índice de massa corporal (kg/m2), média (DP)	27.8 (± 13.1)
Seguro de saúde privado, sim, n (%)	71 (23.0%)
Atividade física, sim, n (%)	159 (51.6%)
Características da dor	
Intensidade da dor no momento, média (DP)	5.8 (± 2.4)
Nível mais forte de dor nas últimas 4 semanas, média (DP)	8.0 (± 2.0)
Nível de dor em média nas últimas 4 semanas, média (DP)	6.6 (± 2.2)
Duração da dor (meses), média (DP)	66.7 (± 100.7)
Intensidade da dor, média (DP)	
Pontuação final do PainDETECT, média (DP)	11.9 (± 7.7)
Dor nociceptiva (0-12), n (%)	173 (56.1%)
Incerto (13-18), n (%)	69 (22.4%)
Sintomas do tipo neuropático (⩾ 19), n (%)	66 (21.4%)
Cold pressor test, prejudicado, n (%)	60 (19.4%)

Os dados são apresentados como média (DP) para variáveis contínuas e como contagens de frequência (%) para variáveis categóricas

Sessenta e seis (21,4%) pessoas com dor musculoesquelética tinham escores do questionário painDETECT ≥ 19, sendo 5 (7,5%) classificados como dor aguda, e 69 (22,4%) pessoas com dor musculoesquelética tinham escores do questionário painDETECT entre 13 e 18 pontos, sendo 12 (17,3%) classificadas como dor aguda. Todas as pessoas com dor musculoesquelética fizeram o questionário painDETECT e o *cold pressor test*. Portanto, não houve valores faltantes para os resultados do questionário painDETECT e do *cold pressor test*. Nenhum evento adverso foi associado ao questionário painDETECT e ao cold pressor test Fig. 1.

A Tabela 2 apresenta os valores de limiar de dor por pressão para pessoas com dor musculoesquelética na região dorsal do antebraço e tibial anterior. O limiar de dor por pressão na tíbia anterior antes do cold pressor test foi reduzido em pessoas com classificação incerta e sintomas do tipo neuropático em comparação com pessoas com dor nociceptiva. O limiar de dor à pressão na região dorsal do antebraço após o cold pressor test foi reduzido em pessoas com classificação incerta e sintomas do tipo neuropático em comparação com pessoas com dor nociceptiva. Não há diferença significativa na comparação intragrupo na região dorsal do antebraço e tibial anterior das pessoas com dor musculoesquelética.

Acurácia diagnóstica do questionário painDETECT

O ponto de corte 12 do questionário painDETECT mostrou sensibilidade, especificidade, acurácia abaixo de 70% e um alto valor preditivo negativo. O ponto de corte 19 do questionário painDETECT apresentou baixa sensibilidade, alta especificidade e alto valor preditivo negativo, apesar da acurácia abaixo de 70% em comparação com o *cold pressor test*. As medidas de sensibilidade, especificidade,

razão de verossimilhança, prevalência da doença, valores preditivos e acurácia em relação ao ponto de corte predefinido do questionário painDETECT para a detecção de comprometimento da modulação condicionada da dor são mostradas na Tabela 3.

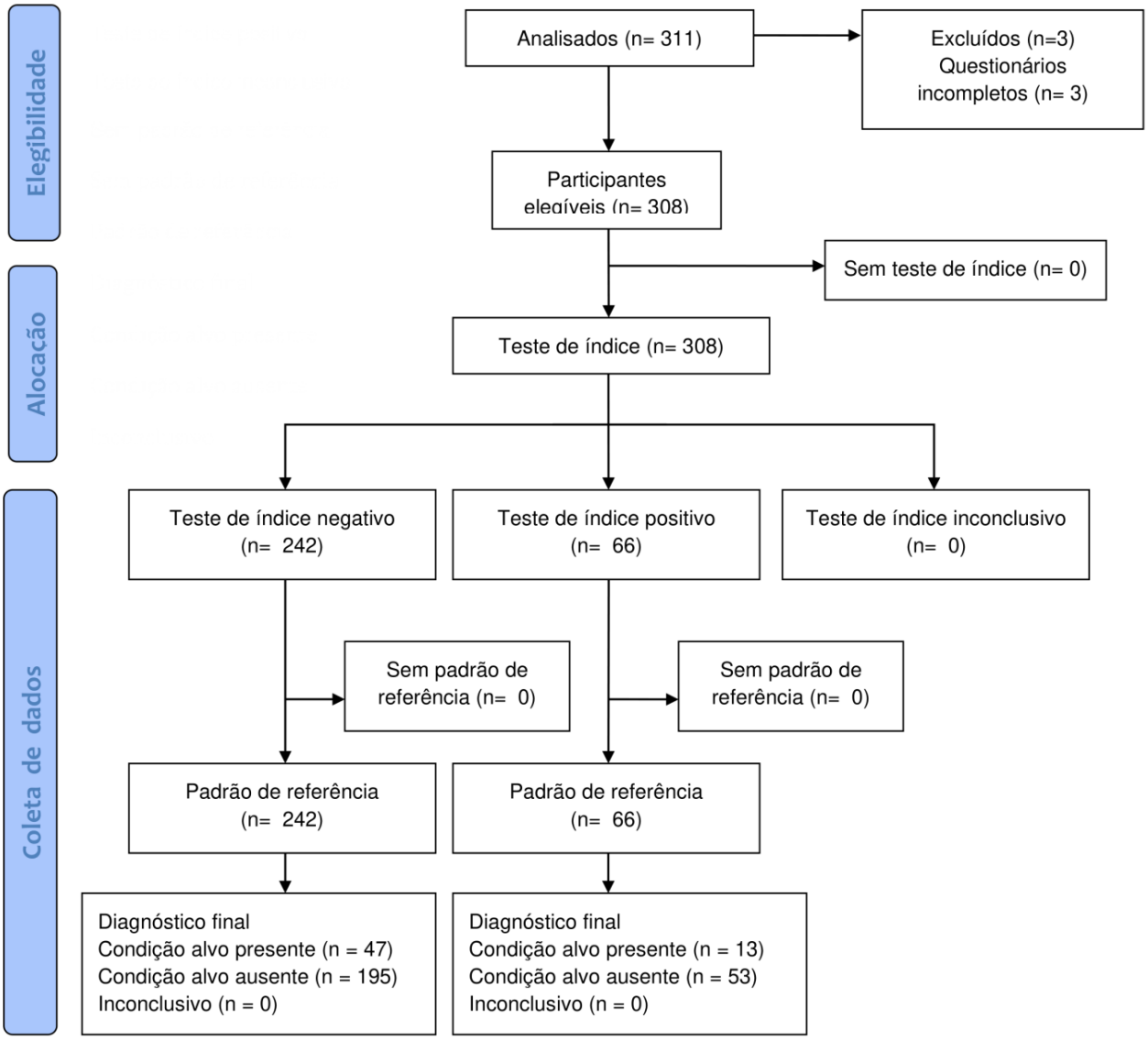

Fig. 1 Fluxograma do estudo

Discussão

Este estudo investigou a acurácia diagnóstica do questionário painDETECT na identificação do comprometimento da modulação da dor condicionada em pessoas com dor musculoesquelética. Nossos achados revelaram que o questionário painDETECT apresentou baixa sensibilidade e alta especificidade para o ponto de corte 19 apenas em comparação com o *cold pressor test*. Nossos dados mostraram altos valores preditivos negativos para ambos os pontos de corte do questionário painDETECT, o que sugere que um teste negativo pode excluir de forma confiável o comprometimento da modulação condicionada da dor nessa população de pessoas com dor musculoesquelética. A baixa prevalência do comprometimento da modulação condicionada da dor na

amostra do estudo provavelmente aumenta o valor preditivo negativo. Dessa forma, muitas pessoas com valores similares no questionário painDETECT foram diagnosticadas com modulação condicionada da dor preservada.

Nossos resultados mostraram que valores abaixo de 19 pontos no questionário painDETECT detectam corretamente a modulação condicionada da dor preservada na maioria das pessoas com dor musculoesquelética. Da mesma forma, um estudo anterior considerou as pontuações acima de 18 no questionário painDETECT como sinais e sintomas relacionados à SC [39]. O questionário painDETECT tem sido usado para a confirmação neurobiológica da sensibilização central em pessoas com características de dor neuropática [40]. Entretanto, um ponto de corte definitivo não é consenso. O ponto de corte de 12 no questionário painDETECT modificado apresenta uma sensibilidade de 61,5% e especificidade de 77,6% na identificação de sinais e sintomas relacionados à SC em pessoas com osteoartrite de joelho [37]. O ponto de corte exato foi sugerido para indicar sinais e sintomas relacionados à SC em pessoas com osteoartrite crônica dolorosa do joelho [22]. No entanto, considerando as medidas de sensibilidade e especificidade relativamente baixas, os autores não recomendaram esse ponto de corte [22]. Da mesma forma, nossos dados sugerem que o ponto de corte de 12 pontos teve acurácia insuficiente para identificar o comprometimento da modulação condicionada da dor em uma amostra heterogênea de pessoas com dor musculoesquelética. Além disso, os baixos valores das razões de verossimilhança para ambos os pontos de corte e a baixa acurácia do ponto de corte 12 limitam a aplicabilidade do questionário painDETECT para identificar o comprometimento da modulação condicionada da dor em pessoas com dor musculoesquelética.

Os sintomas do tipo neuropático estão ligados a sinais e sintomas periféricos e relacionados à SC. Algumas variantes genéticas podem ser um modulador essencial no desenvolvimento de sinais e sintomas relacionados à SC na dor neuropática [41]. Ainda assim, os sinais e sintomas relacionados à SC se manifestam mais em condições dolorosas com o componente neuropático [42, 43]. Muitas estratégias, como a modulação condicionada da dor, poderiam avaliar as características clínicas dos sinais e sintomas relacionados à SC. A modulação condicionada da dor é um preditor no desenvolvimento e tratamento da dor neuropática [44], mas pode ter um desempenho diferente em condições de dor neuropática. Gagné et al. sugeriram que a presença de dor neuropática leva a uma diminuição da modulação condicionada da dor ao longo do tempo [45]. A síndrome do túnel do carpo [13] e a neuropatia periférica dolorosa [15] são exemplos de comprometimento da modulação condicionada da dor. Por outro lado, pessoas com neuropatia diabética dolorosa tinham uma modulação condicionada da dor preservada, apesar da duração da dor [46]. Portanto, a relação entre a modulação condicionada da dor e a dor neuropática pode ser uma característica específica dessa população.

Nosso estudo fornece novos *insights* para implementação no uso clínico e em outros estudos. O questionário PainDETECT pode ser usado como uma estratégia de triagem inicial por fisioterapeutas e outros profissionais de saúde para rastrear sintomas do tipo neuropático em pessoas com dor musculoesquelética. Características semelhantes de dor estão presentes em condições de dor musculoesquelética. Usando o questionário painDETECT, o fisioterapeuta pode classificar as pessoas de acordo com o fenótipo da dor. Da mesma forma, o fisioterapeuta pode oferecer

estratégias de tratamento adequadas a um determinado indivíduo.

Os pesquisadores devem usar instrumentos com alta acurácia para avaliar a presença de sinais e sintomas relacionados à SC e sintomas do tipo neuropático para confirmar os achados do presente estudo. Além disso, estudos futuros devem se concentrar em métodos para caracterizar pragmaticamente as pessoas com comprometimento da modulação condicionada da dor para facilitar a tomada de decisão dos fisioterapeutas. Por fim, a acurácia diagnóstica do painDETECT é apenas uma das considerações ao determinar uma ferramenta de triagem para dor musculoesquelética. Portanto, outros aspectos devem ser considerados.

Tabela 2 Comparação dos valores de limiar de dor entre pessoas com sintomas do tipo neuropático, dor nociceptiva e classificação incerta

Características	Dor nociceptiva n = 173	Incerta n =69	Sintomas do tipo neuropático n = 66	ANOVA	Grupos de comparação	Valor de *p*
Linha de base						
Algometria do dorso do antebraço (kgf)	4,1 (1,5)	3,6 (1,2)	3,6 (1,2)	5,290	Nociceptiva *versus* Incerta	0,029
					Nociceptiva *versus* Neuropática	0,024
Algometria do tibial anterior (kgf)	4,6 (1,7)	4,2 (1,7)	3,5 (1,4)	8,673	Nociceptiva *versus* Neuropática	<0,001
Após *Cold Pressor Test*						
					Nociceptiva *versus* Incerta	0,42
Algometria do dorso do antebraço (kgf)	4,4 (1,6)	3,9 (1,6)	3,6 (1,3)	8,417	Nociceptiva *versus* Neuropática	<0,001
Algometria do tibial anterior (kgf)	4,9 (1,9)	4,5 (2,0)	4,0 (1,5)	3,961	Nociceptiva *versus* Neuropática	0,03
Mudança intragrupo						
Algometria do dorso do antebraço (kgf)	0,3 (1,2)	0,3 (1,1)	-0,0 (1,1)	1,829	-	0,162
Algometria do tibial anterior (kgf)	0,3 (1,3)	0,3 (1,1)	0,4 (1,1)	0,221	-	0,802

Os dados são apresentados como uma média (DP) para variáveis contínuas

Tabela 3 Sensibilidade, especificidade, valor preditivo positivo, valor preditivo negativo e acurácia são os dois pontos de corte predefinidos do questionário painDETECT para detectar o comprometimento da modulação condicionada da dor

	painDETECT 12	painDETECT 19
Sensibilidade %, (IC 95%)	46,6% (33,6 – 60,0)	21,6% (12,0 – 34,2)
Especificidade %, (95% CI)	43,1% (36,8 – 49,5)	78,6% (73,0 – 83,5)
Razão de probabilidade positiva (IC 95%)	0,8 (0,6 – 1,1)	1,0 (0,5 – 1,7)
Razão de verossimilhança negativa (IC de 95%)	1,2 (0,9 – 1,6)	1,0 (0,8 – 1,1)
Prevalência de CPM prejudicada %, (IC 95%)	19,4% (15,2 – 24,3)	19,4% (15,2 – 24,3)
Valor preditivo positivo (IC 95%)	16,5% (12,9 – 21,0)	19,7 (12,5 – 29,5)
Valor preditivo negativo (IC 95%)	76,9% (71,7 – 81,5)	80,5% (78,1 – 82,7)
Precisão (IC 95%)	43,8% (38,2 – 49,5)	67,5% (61,9 – 72, 7)

Abreviação: MCD Modulação condicionada da dor

Pontos fortes e limitações do estudo

Reconhecemos os pontos fortes e as limitações do presente estudo. Primeiro, a originalidade deste estudo verificou a acurácia diagnóstica do questionário painDETECT para detectar o comprometimento da modulação condicionada da dor. Em segundo lugar, usamos a modulação condicionada da dor, uma medida confiável [47] por meio de um teste psicofísico (cold pressor test), para detectar o comprometimento da

modulação condicionada da dor usando duas regiões anatômicas diferentes para garantir a classificação adequada dos participantes. Por fim, o grande tamanho da amostra pode ser considerado um ponto forte deste estudo. A principal limitação do estudo é que o cold pressor test e o questionário painDETECT não são padrão-ouro para diagnosticar o comprometimento da modulação condicionada da dor e dor neuropática, respectivamente. Treede sugeriu que um experimento com hiperalgesia secundária induzida por injeção intradérmica de capsaicina é a única ocorrência documentada de sensibilização central que atende à sua definição formal [48]. No entanto, o *cold pressor test* é o método mais comumente usado [35] e tem confiabilidade intra-sessão de boa a excelente em pessoas saudáveis e com dor crônica [49] para avaliação da modulação condicionada da dor. Além disso, o questionário painDETECT pode identificar sintomas do tipo neuropático, mas a classificação neuropática positiva no painDETECT é insuficiente para classificar a neuropatia [50].

Conclusão

O questionário painDETECT parece ser valioso para excluir pessoas com dor musculoesquelética e comprometimento da modulação condicionada da dor.

Abreviações

ANOVA Análise de variância
IC Intervalo de confiança
SC Sensibilização central
MCD Modulação condicionada da dor
JASP Jeffreys's Amazing Statistics Program
Kg Quilogramas
Kgf Quilogramas-força
Kg/m2 Quilogramas-força por metro quadrado
DP Desvio padrão
STARD Standards for Reporting of Diagnostic Accuracy Studies

Informações suplementares

A versão on-line contém material suplementar disponível em https://doi.org/10.1186/s40945-023-00171-8 .

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Não se aplica.

Contribuições dos autores

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Disponibilidade de dados e materiais

Não se aplica.

Declarações

Aprovação ética e consentimento de participação
A pesquisa envolvendo seres humanos obedeceu a todas as regulamentações nacionais relevantes, políticas institucionais e está de acordo com os princípios da Declaração de Helsinque (conforme alterada em 2013), e foi aprovada por um comitê de ética em pesquisa equivalente (número: 02228818.0.3001.5258). O consentimento informado foi obtido de todos os indivíduos incluídos neste estudo.

Consentimento para publicação

Não aplicável.

Interesses conflitantes

Cada autor certifica que ele ou um membro de sua família imediata não tem nenhuma associação comercial (ou seja, consultorias, propriedade de ações, participação acionária, acordos de patente/licenciamento, etc.) que possa representar um conflito de interesses em relação ao manuscrito enviado.

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Nota do editor

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