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Advances in chronic pain treatment

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Published in
Frontiers in Medicine

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ISSN 1664-8714
ISBN 978-2-8325-5564-4
DOI 10.3389/978-2-8325-5564-4

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Advances in chronic pain treatment

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Citation

Ferrer-Peña, R., Goicoechea, C., Lipnik-Stangelj, M., eds. (2024). *Advances in chronic pain treatment*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5564-4

Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 04 October 2024
DOI 10.3389/fmed.2024.1496449

Check for updates

OPEN ACCESS

EDITED AND REVIEWED BY
Arch Mainous,
University of Florida, United States

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RECEIVED 14 September 2024
ACCEPTED 23 September 2024
PUBLISHED 04 October 2024

CITATION
Ferrer-Peña R, Lipnik-Stangelj M and Goicoechea C (2024) Editorial: Advances in chronic pain treatment.
Front. Med. 11:1496449.
doi: 10.3389/fmed.2024.1496449

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Editorial: Advances in chronic pain treatment

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KEYWORDS

chronic pain, neurophysiological mechanisms, risk factors, neuromodulation, personalized & precision medicine (PPM), biobehavioral, movement

Editorial on the Research Topic
Advances in chronic pain treatment

Introduction

Chronic pain is a multifaceted condition that affects millions globally (1), often persisting beyond 3 months and significantly impairing individuals' quality of life (2). In recent decades, significant advances have been made in understanding the pathophysiology of chronic pain, laying the groundwork for the development of new therapies and therapeutic approaches. This progress has been largely driven by advances in neuroscience, providing a deeper understanding of how the brain and central nervous system process pain (3). The development of neuroimaging techniques has allowed scientists to observe directly the alterations in brain activity associated with chronic pain, identifying abnormal patterns of neural activation and desynchronization that perpetuate pain perception (4, 5).

This growing understanding of chronic pain has led to the integration of multiple disciplines in its approach, from medicine and psychology to biotechnology and engineering (6). This multidisciplinary approach is crucial for addressing the complexity of this condition, enabling the development of strategies that not only focus on relieving pain but also address its underlying causes, thus optimizing long-term outcomes for patients (7).

Neurophysiological mechanisms and risk factors

Understanding the neurophysiological mechanisms underlying chronic pain remains a priority within the field. Pinilla-Fernández et al. explore the neurobiological underpinnings of chronic neuropathic pain using advanced neuroimaging techniques. Where they quantified the difference in brain metabolite concentrations in whiplash-associated disorders (WAD) within the anterior cingulate and dorsolateral prefrontal

cortex, and identified key metabolites associated with chronic neuropathic pain components during chronic WAD.

Additionally, Diao et al. employ a genetic approach to investigate modifiable risk factors in the development and progression of knee osteoarthritis. Through a Mendelian randomization study, they highlight the causal relationships between these risk factors and the disease, underscoring the importance of addressing modifiable elements in both preventive and therapeutic strategies. Together, these studies reinforce the need for a multifaceted approach to managing chronic pain, integrating neurophysiological insights with a focus on modifiable risk factors to optimize patient outcomes.

Neuromodulation and pain management

One of the central themes in recent advances in chronic pain treatment is the role of neuromodulation in managing chronic pain conditions. Chang et al. provide a comprehensive review of the effectiveness of transcranial alternating current stimulation (tACS) in managing chronic pain. While results vary across different studies, this review highlights the potential of tACS as a non-invasive neuromodulatory tool, particularly for conditions resistant to conventional therapies. Moreover, Escobar-Sánchez et al. explore the long-term effects of high-frequency stimulation (HFS) on pain and sensitivity in healthy subjects. Their study illustrates significant bilateral changes in mechanical and thermal sensitivity after HFS, particularly in cold sensitivity, which persisted long after the stimulation ended. These findings suggest that demographic characteristics, such as age and gender, may influence the efficacy of neuromodulatory interventions. As research continues to explore pain mechanisms, these insights will be crucial for developing more targeted and effective therapies.

Other innovative therapies and technology integration

The exploration of innovative therapies and technologies remains a critical focus in the current scientific landscape. Li et al. review the latest developments in biomimetic nanotechnology for drug delivery, particularly emphasizing its application in treating rheumatoid arthritis. They highlight the potential of biomimetic nano-systems to revolutionize the treatment of chronic inflammatory conditions by enhancing the precision and efficiency of drug delivery. This approach could significantly improve the management of diseases like rheumatoid arthritis, where targeted drug delivery is essential to improve therapeutic efficacy, minimize systemic side effects, and thus optimize patient outcomes.

Additionally, Doménech-García et al. investigate the complex interplay between placebo and nocebo effects in invasive treatments, such as percutaneous needle electrolysis and dry needling, for patients with patellar tendinopathy. Their research sheds light on the intricate psychological factors involved in chronic pain management, demonstrating how patient expectations can profoundly influence treatment outcomes.

Personalized therapeutic approaches

The importance of personalized approaches in treating chronic pain is another significant theme within recent research. Escobar-Sánchez et al. highlight how different stimulation modalities can lead to variable changes in pain perception and sensitivity, emphasizing the necessity of tailoring pain management strategies to the specific characteristics of each patient. Similarly, Sreckovic et al. explore the role of peripheral nerve blocks in managing chronic post-surgical pain (CPSP) after knee arthroplasty. Their findings suggest that nerve blocks, such as the adductor canal block and interspace between the popliteal artery and capsule of the posterior knee block, significantly reduce opioid consumption and the incidence of CPSP, demonstrating that personalized regional analgesia can effectively improve postoperative outcomes and reduce long-term pain.

On the other hand, Del Piccolo et al. introduce the INTEGRO protocol, an innovative integrated psychotherapeutic intervention designed for fibromyalgia (FM) management. This protocol combines Cognitive Behavioral Therapy, Acceptance and Commitment Therapy, and somatic experiential techniques to address the complex, multifaceted nature of FM. Through a personalized approach that includes psychoeducation, emotion regulation, and self-efficacy enhancement, the INTEGRO protocol has demonstrated its effectiveness in reducing FM-related pain and improving the health-related quality of life in patients. Moreover, La Touche et al. introduce the BioPMovQ, a novel instrument designed to assess the relationship between pain and movement from a biobehavioral perspective. These studies collectively highlight the critical need for personalized therapeutic approaches in chronic pain treatment, emphasizing the role of individualized strategies in optimizing patient outcomes.

Integrating clinical theory and practice

In addition to personalized treatments, it is also relevant to highlight the integration of theoretical knowledge into clinical practice advances. Zhai et al. revisit and refine the theory of trigger points and their role in musculoskeletal pain, offering a comprehensive review that emphasizes the importance of understanding muscle pain patterns in clinical practice considering biomechanics, kinesiology and compensatory mechanisms. Their work advocates for a more nuanced application of trigger point theory in clinical settings, emphasizing that a deeper grasp of these mechanisms can lead to improved patient outcomes.

Conclusion

The articles featured in this analysis collectively advance our understanding of chronic pain and its management. By integrating neuromodulation, personalized therapies, theoretical insights, and innovative technologies, these studies offer a comprehensive overview of the current landscape in chronic pain treatment. The findings presented here not only deepen our understanding

of chronic pain but also pave the way for future research and clinical applications that could significantly enhance patient care and outcomes.

Author contributions

RF-P: Writing – review & editing, Writing – original draft. ML-S: Writing – original draft, Writing – review & editing. CG: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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References

1. Zimmer Z, Fraser K, Grol-Prokopczyk H, Zajacova A. A global study of pain prevalence across 52 countries: examining the role of country-level contextual factors. *Pain.* (2022) 163:1740–50. doi: 10.1097/j.pain.0000000000002557

2. Hadi MA, McHugh GA, Closs SJ. Impact of chronic pain on patients' quality of life: a comparative mixed-methods study. *J Patient Exp.* (2019) 6:133–41. doi: 10.1177/2374373518786013

3. Chen ZS. Decoding pain from brain activity. *J Neural Eng.* (2021) 18:051002. doi: 10.1088/1741-2552/AC28D4

4. Bosma RL, Hemington KS, Davisa KD. Using magnetic resonance imaging to visualize the brain in chronic pain. *Pain.* (2017) 158:1192. doi: 10.1097/j.pain.0000000000000941

5. Martucci KT, MacKey SC. Neuroimaging of pain: human evidence and clinical relevance of central nervous system processes and modulation. *Anesthesiology.* (2018) 128:1241–54. doi: 10.1097/ALN.0000000000002137

6. Driscoll MA, Kerns RD. Integrated, team-based chronic pain management: bridges from theory and research to high quality patient care. *Adv Exp Med Biol.* (2016) 904:131–47. doi: 10.1007/978-94-017-7537-3_10

7. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet.* (2021) 397:2082–97. doi: 10.1016/S0140-6736(21)00393-7

frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 20 December 2023
DOI 10.3389/fneur.2023.1323520

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OPEN ACCESS

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RECEIVED 18 October 2023
ACCEPTED 06 December 2023
PUBLISHED 20 December 2023

CITATION
Chang MC, Briand M-M, Boudier-Revéret M and Yang S (2023) Effectiveness of transcranial alternating current stimulation for controlling chronic pain: a systematic review.
Front. Neurol. 14:1323520.
doi: 10.3389/fneur.2023.1323520

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Effectiveness of transcranial alternating current stimulation for controlling chronic pain: a systematic review

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Background: Chronic pain is common, disruptive, and often treatment-resistant. Hence, researchers and clinicians seek alternative therapies for chronic pain. Transcranial alternating current stimulation (tACS) is an emerging neuromodulation technique that non-invasively modulates neural oscillations in the human brain. tACS induces pain relief by allowing the neural network to restore adequate synchronization. We reviewed studies on the effectiveness of tACS in controlling chronic pain.

Methods: The PubMed, SCOPUS, Embase, and Cochrane Library databases were systematically searched for relevant studies published until December 6, 2023. The key search phrase for identifying potentially relevant articles was [(Transcranial Alternating Current Stimulation OR tACS) AND pain]. The following inclusion criteria were applied for article selection: (1) studies involving patients with chronic pain; (2) tACS was applied for controlling pain; and (3) follow-up evaluations were performed to assess the degree of pain reduction after the application of tACS.

Results: We identified 2,330 potentially relevant articles. After reading the titles and abstracts and assessing eligibility based on the full-text articles, we included four articles in our review. Among the included studies, tACS was used for fibromyalgia in one study, low back pain (LBP) in two studies, and migraine in one study. In the study on fibromyalgia, it did not show a better pain-reducing effect of tACS compared with sham stimulation. Two studies on LBP showed conflicting results. In migraine, tACS showed a positive pain-reducing effect 24–48 h after its application.

Conclusion: There is insufficient research to draw a conclusive judgment on the effectiveness of tACS in controlling chronic pain. More studies across various chronic pain-related diseases are required for a definitive conclusion.

KEYWORDS

transcranial alternating current stimulation, chronic pain, fibromyalgia, low back pain, migraine, treatment, review

Introduction

Chronic pain is pain that persists for more than 3 months or after complete healing, which is a leading cause of disability and disease worldwide (1, 2). Approximately 20% of the adult population experiences chronic pain, with 8% of individuals reporting severe pain that disrupts their life and work activities (3). To manage chronic pain, various therapeutic methods have been applied, including physical therapy, psychotherapy, medication, procedures, and surgery (1, 2). However, despite these treatments, chronic pain often remains uncontrolled.

The brain plays a fundamental role in the processing of pain (4). Several previous studies using electroencephalography (EEG) and magnetoencephalography (MEG) demonstrated that chronic pain is closely associated with abnormal neuronal oscillations (5–8). The peak frequency of neuronal oscillations measured by EEG or MEG was lower in patients with chronic pain compared with that of healthy controls (5–8). Specifically, changes in neural oscillations at gamma (30–100 Hz) frequencies in prefrontal brain area are related to chronic pain (9). The modulation of neural oscillations has been suggested to be a promising novel therapeutic approach for controlling chronic pain.

Transcranial alternating current stimulation (tACS) is an emerging neuromodulation technique that non-invasively modulates neural oscillations in the human brain (10–12). During the application of tACS, a weak alternating sinusoidal current is administered to the scalp with the aim of synchronizing neural oscillations at the stimulation frequency, thereby enhancing their amplitude and causing a new balance by forcing the neural network to restore adequate synchronization (10–12). This neural modulation by tACS was proposed to induce pain relief.

Thus far, some clinical trials have been conducted to investigate whether tACS has a pain-reducing effect in patients with chronic pain (13–17). In this study, we review previous studies on the effectiveness of tACS in controlling chronic pain and integrate their results to draw a comprehensive conclusion on the therapeutic possibility of tACS for pain reduction.

Methods

This systematic review conformed to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analysis. The protocol was registered on the international platform of registered systematic reviews protocols (registration number: INPLASY2023120012).

The population, intervention, comparison, and outcome (PICO) setting of the current systematic review was as follows: P: patients with chronic pain; I: tACS combined with or without other therapies for controlling pain; C: placebo or sham stimulation; and O: pain intensity. Two authors (MC and SY) searched for relevant studies published until December 6, 2023, in the PubMed, SCOPUS, Embase, and Cochrane Library databases (Supplementary material 1). The key search phrase for identifying potentially relevant articles was [(Transcranial Alternating Current Stimulation OR tACS) AND pain]. The following inclusion criteria were applied for the selection of articles: (1) patients with chronic pain; (2) tACS was applied for controlling pain; and (3) follow-up evaluations were performed after tACS stimulation to assess the degree of pain reduction after the application of tACS. We excluded the following studies: (1) review articles; (2) animal studies; and (3) conference abstracts or presentations.

After duplicate publications were deleted, two reviewers (MC and SY) independently evaluated potentially eligible studies that were identified by our search. Articles were screened for eligibility based on a review of the title and abstract, and disagreements were resolved by consensus. The full texts of eligible articles were accessed and read independently by the two reviewers (MC and SY).

The risk of bias of selected studies was evaluated using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions to assess potential bias (18). The domains to evaluate the risk of bias were as follows: (1) random sequence generation and allocation concealment (selection bias); (2) blinding of participants and personnel (performance bias); (3) blinding of outcome assessment (detection bias); (4) incomplete outcome data (attrition bias); (5) selective reporting (reporting bias); and (6) other biases. Two independent reviewers performed these evaluations (MC and SY), and discrepancies were resolved through discussion.

Results

Search results

A total of 2,405 articles were identified using the search terms. Of these, 740 duplicates were excluded from further analysis. After reading the titles and abstracts, 1,653 articles were excluded because they did not meet the inclusion criteria. Subsequently, 12 full-text articles were retrieved to verify study eligibility, and a total of four publications were finally included in this review (Figure 1) (13, 14, 16, 17). These four publications were all randomized controlled trials (RCTs) (13, 14, 16, 17). Among these four studies, two were conducted under a randomized, double-blind, crossover design (13, 17). Table 1 presents the characteristics of the included articles, and Table 2 presents the application methods for tACS and combined treatments with tACS. Among four included studies, tACS was applied for fibromyalgia in one study (16), low back pain (LBP) in two studies (13, 17), and migraine in one study (14).

Fibromyalgia

In 2022, Lin et al. conducted an RCT to evaluate the effect of tACS on the left primary motor cortex (M1) for the management of chronic pain from fibromyalgia (16). Thirty-eight patients having a history a widespread pain with ≥3 months duration were recruited and randomly allocated to the tACS ($n = 19$) and sham stimulation ($n = 19$) groups. tACS was conducted with a daily session of 20 min of stimulation of 1 mA at 50 Hz (duty cycle with an on time of 2 s and off time of 8 s) over the left M1 (C3 position in the 10/20 system for the EEG electrode positions) for 10 sessions in 2 weeks. For the administration of the electrical current, a 4×1 ring electrode configuration was used. The pain severity and physical function were assessed using the numeric rating scale (NRS) and the fibromyalgia impact questionnaire (FIQ) at baseline and after 2 weeks of tACS treatment. Additionally, the Beck Anxiety Inventory, Beck Depression

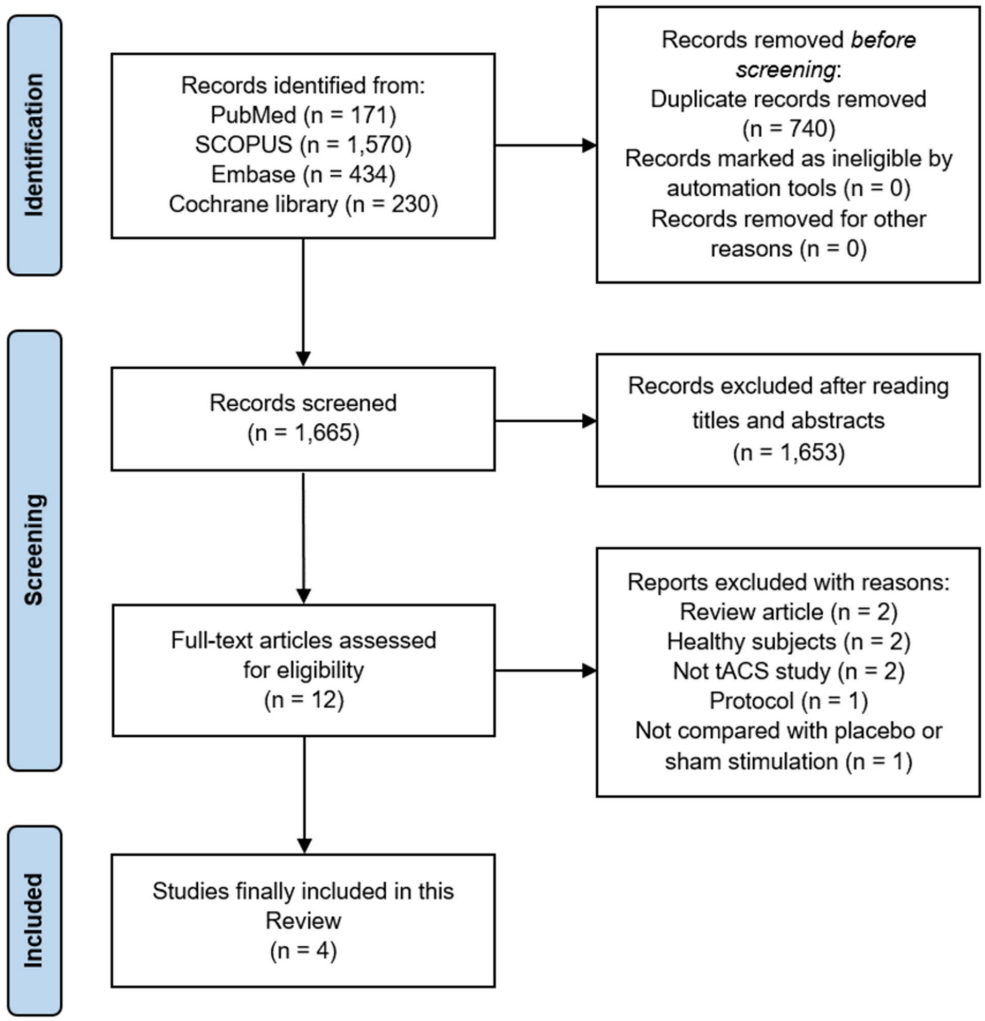

FIGURE 1
PRISMA flow diagram. tACS, Transcranial alternating current stimulation.

Inventory-II, and Pittsburgh Sleep Quality Index (PSQI) were checked. During the study, one patient in the tACS group and two in the sham stimulation group dropped out. After 10 sessions of tACS and sham stimulation, there were no significant differences in the changes in all the measurements between the groups. After tACS, various adverse events, including headache, scalp pain, stinging, itch, burning sensation, drowsiness, and difficulty concentrating, were reported. However, the severity of all the adverse events was mild, and the occurrence rate was not different from the sham stimulation group.

Low back pain

In 2019, Ahn et al. (13) performed a randomized, double-blind, crossover design study to investigate the effect of tACS on controlling LBP. They recruited 20 patients with chronic LBP persisted at least 5 months and randomly allocated them into two groups (tACS and sham stimulation groups). After the first session was completed, all the patients had a washout interval of 1–3 weeks. They were then crossed over to the other groups and had a second session. Two stimulating electrodes (5 cm × 5 cm each) were placed at the bilateral frontal lobe (F3 and F4) and delivered a sinusoidal waveform with 1 mA amplitude for 40 min. The return electrode (5 cm × 7 cm) was placed at Pz (medial parietal region). At pretreatment and after completing each session, the Defense and Veterans Pain Rating Scale (DVPRS, from 0 to 10, 0 = no pain and 10 = worst imaginable pain, similar to the NRS), Oswestry Disability Index (ODI), and enhancement of alpha oscillation were measured. After tACS, the pain severity measured by DVPRS was significantly reduced compared to sham stimulation, but ODI was not. The increase in alpha oscillations was significantly higher after tACS compared to sham stimulation.

In the same year, Prim et al. (17) conducted a randomized, double-blind, crossover design study in 20 patients with chronic LBP (pain duration: at least 6 months). The included patients were divided into two groups (10 patients per group). The schedule for the application of tACS, areas that place the electrodes, and electrode type were the same as in Ahn et al.'s study on the forehead. Prim et al. defined the responders as patients who had a decrease of ≥2 points on the DVPRS after completing the stimulation session. Twice as many patients reported being responders after tACS treatment vs. after sham stimulation, but no significant difference was found. They also checked the degree of adverse effects, including headache, neck pain, scalp

TABLE 1 Characteristics of the included studies.

#	First author	Published year	No. of patient	Age, years (mean ± SD)	Disease	Pain duration of patients	Study type	Outcome parameters	Results
1	Lin (16)	2022	35 (tACS: sham = 18:17)	tACS: 48.3 ± 13.6 Sham: 48.9 ± 12.3	Fibromyalgia	≥3 months	RCT	NRS, FIQ, BAI, BDI-II, and PSQI	- All the measured outcomes were not significantly different between the tACS and sham stimulation groups.
2	Ahn (13)	2019	20	Age range: 18–65, no information on mean	Low back pain	≥5 months	Randomized, double-blind, crossover design	DVPRS, ODI, and EEG	- The DVPRS score was significantly lower after tACS than after sham stimulation, but the ODI was not. - The increase in alpha oscillations was significantly higher after tACS compared to sham stimulation.
3	Prim (17)	2019	20	43.0 ± 13.4	Low back pain	≥6 months	Randomized, double-blind, crossover design	DVPRS	- No significant difference was found between tACS and sham stimulation.
4	Antal (14)	2020	25 (tACS: sham = 16:9)	tACS: 31.1 ± 8.9 Sham: 28.1 ± 10.5	Migraine	≥6 months	RCT	NRS	- The reduction of NRS at 2 and 4 h after stimulation was significantly higher in the tACS group than in the sham stimulation group.

tACS, Transcranial alternating current stimulation; SD, Standard deviation; RCT, Randomized controlled trial; NRS, Numeric rating scale; FIQ, Fibromyalgia impact questionnaire; BAI, Beck Anxiety Inventory; PSQI, Pittsburgh Sleep Quality Index; DVPRS, Defense and Veterans Pain Rating Scale; ODI, Oswestry Disability Index; and EEG, electroencephalogram.

pain, tingling, itching, ringing/buzzing noise, burning sensation, local redness, sleepiness, trouble concentrating, improved mood, worsening of mood, dizziness, and flickering lights, with numeric scores. The significant difference in score for each side effect was not shown between tACS and sham stimulation.

Migraine

In 2020, Antal et al. (14) recruited 40 patients with chronic migraine (pain duration: ≥6 months), and they were randomly allocated to the tACS (25 patients) and sham stimulation (15 patients) groups. Among these patients, 25 patients—16 in the tACS group and nine in the sham stimulation group—completed the study. The study was conducted over the course of 6 weeks. Patients were asked to write a headache diary during the study period. During the study, the frequency of the migraine attacks, duration of the pain, and use of analgesics were recorded. The pain degree was also measured with NRS at the onset of a migraine attack as well as 1, 2, 4, 8, 24, and 48 h thereafter. tACS or sham stimulation was applied by the patient at home. The stimulation was applied at the beginning of the migraine attack. The stimulating electrode (4 cm × 4 cm) was placed over the occipital lobe (Oz) and the return electrode (5 cm × 7 cm) over the Cz electrode position. tACS with 0.4 mA was applied for 15 min. During the study, 65 migraine attacks were treated in 16 patients in the tACS group (mean: 4.06 attacks/patient) and 37 in nine patients in the sham stimulation group (mean: 4.11 attacks/patient). In the tACS group, 27 of the 65 migraine attacks were treated with oral medications within 2 h after the stimulation, compared to 14 of the 37 attacks in the sham stimulation group. During the migraine attacks without taking oral medications, the pain disappeared within 2 h post-stimulation in 14 of the 38 attacks in the tACS group but in none of the 23 attacks in the

TABLE 2 Application methods for tACS treatment and combined treatments with tACS.

#	First author	Simulation site	Intensity (mA)	Duration (min)	Frequency (Hz)	No. of sessions	Combined treatments with tACS	Treatment received by control group
1	Lin (16)	M1	1	20	50	10	No combined treatment.	Sham stimulation
2	Ahn (13)	Bilateral F-lobe (F3, F4)	1	40	10	1 per study arm	No combined treatment.	Sham stimulation
3	Prim (17)	M1	1	40	10	1 per study arm	No combined treatment.	Sham stimulation
4	Antal (14)	O-lobe (Oz)	0.4	15	140	1 (at the beginning of the migraine attack)	The included patients were allowed to take their regular acute migraine medications	Sham stimulation and regular acute migraine medications

tACS, Transcranial alternating current stimulation; M1, Primary motor cortex; F-lobe, Frontal lobe; and O-lobe, Occipital lobe.

sham stimulation group, with a statistically significant intragroup difference. The rate of terminated migraine attacks that did not require acute rescue medication was significantly higher in the tACS group (21.5%) than in the sham stimulation group (0%). The pain severity measured with NRS was significantly lower after tACS than after sham stimulation in 2 and 4 h after the stimulation.

Risk of Bias

All four included studies had a low risk of bias in the domains of allocation concealment, blinding of participants and personnel, and selective reporting (Figure 2). In random sequence generation, three studies had a low risk of bias. In the domain of blinding outcome assessment, only one study had a low risk of bias, and in the domain of incomplete outcome data, two studies had a low risk of bias. Three studies had a low risk of bias in the domain of other biases. Among the 28 domains across all four included studies, 21 domains (75.0%) were determined to be low risk. The inter-rater agreement for the determination of potential bias of each study was 0.900 ($p < 0.001$) according to the kappa index.

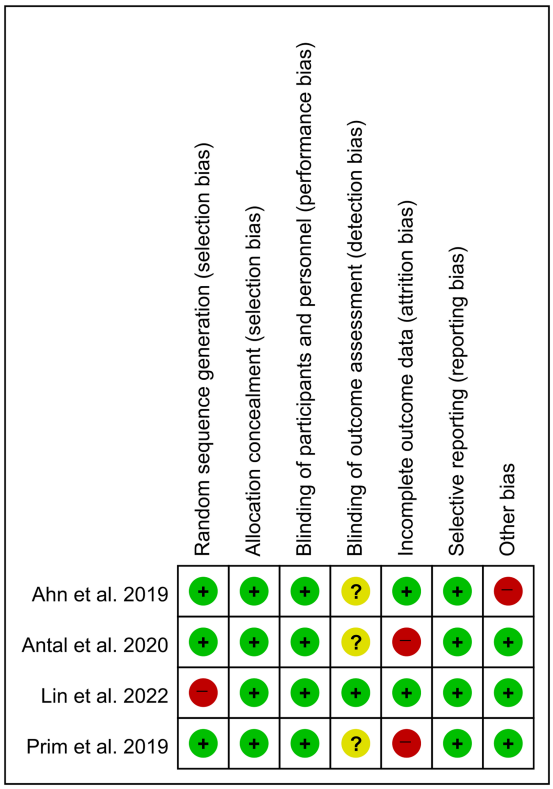

FIGURE 2
Risk of bias summary.

Discussion

In this review of tACS for chronic pain, we found four published articles in that met our inclusion criteria (13, 14, 16, 17). The patients included in the previous studies had fibromyalgia in one study (16), LBP in two studies (13, 17), and migraine in one study (14).

Patients with chronic pain exhibit impaired alpha oscillations (13, 19). It is known that pain perception suppresses alpha oscillations (13, 19). Previous studies found that the amplitude of alpha oscillations in the brain was negatively correlated with the severity of chronic pain (20–22). tACS can modulate neural oscillations by applying oscillating electrical currents (10–12). The enhanced alpha oscillations by tACS can be suggested to induce pain relief. Additionally, in patients with chronic pain, abnormal activation of the thalamic nuclei, insula, anterior cingulate, and sensory and prefrontal cortices was observed during pain processing (23, 24). The previous studies using EEG found increased theta rhythm mainly located in the anterior cingulate and frontal cortex, which are part of the thalamocortical circuit. The thalamocortical circuit plays a crucial role in processing and transmitting pain signals in the human brain (25, 26). Abnormal activation of the thalamocortical circuit is considered a key pathology inducing the development of chronic pain (25, 26). Therefore, chronic pain is interpreted as the result of thalamocortical dysrhythmia (25). Low-intensity alternating currents produced by tACS could modulate abnormal neural activation within the thalamocortical circuit, which is supposed to be helpful for alleviating chronic pain (15).

However, contrary to our expectations, the results of our study that integrated the findings of four previous studies were conflicting (13, 14, 16, 17). In the study on fibromyalgia (16), it did not show a better pain-reducing effect of tACS compared with sham stimulation

(16). The two studies on LBP showed opposite results (13, 17). The study of Ahn et al. (13) showed a positive pain-reducing effect of tACS, but study of Prim et al. (17) did not find any significant difference between the pain-reducing effect of tACS and that of sham stimulation. Regarding migraine, the study reported that tACS was helpful for terminating migraine attacks and reducing pain severity during migraine attacks (14). The conflicting results hinder the conclusion of the effectiveness of tACS for controlling chronic pain.

Responses to tACS can vary among individuals. Factors such as the brain anatomy, exact placement of electrodes, and brain state during stimulation would influence the pain-reducing effect of tACS (27). Also, patients suffering from pain exhibit a wide range of pain patterns and characteristics. The individual variation in tACS effects might have contributed to the conflicting results in previous studies.

Additionally, even if the previous studies demonstrated a positive pain-reducing effect of tACS (13, 14), patients with LBP reported only immediate effects after tACS sessions (13). The pain relief effect of tACS in patients with migraines lasted only 24–48 h following tACS treatment (14). The long-term effect of tACS was not reported or evaluated in the previous studies. Therefore, studies investigating the effect of tACS on controlling chronic pain are required.

In the previous studies, the number of stimulation sessions varied in each study. The study of Lin et al. (16) applied tACS with 10 sessions, but the other studies used tACS with a single session (13, 14, 17). Also, the brain area to which tACS was applied and the intensity of current stimulation varied across the previous studies (13, 14, 16, 17). Further research should be conducted to establish the most effective tACS treatment protocol for controlling chronic pain.

In this review, we investigated the effectiveness of tACS in controlling chronic pain. We reviewed four studies (13, 14, 16, 17), among which two reported a positive effect on pain control (13, 14), while the remaining two studies reported negative results (16, 17). Furthermore, even if the positive pain-reducing effect of tACS was reported in two studies, it was only an immediate or short-term pain-relieving effect (13, 14). We think that there is still insufficient research to draw a conclusive judgment on the effects of tACS on controlling chronic pain. For a definitive conclusion, more studies across various chronic pain-related diseases are required. Also, studies for determining the optimal stimulation area, intensity, duration, and frequency for tACS treatment should be conducted in the future.

Author contributions

MC: Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Project administration, Visualization, Investigation, Methodology, Resources. M-MB: Methodology, Writing – review & editing. MB-R: Formal analysis, Methodology, Validation, Writing – review & editing. SY: Conceptualization, Formal analysis, Project administration, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (no. 00219725).

Conflict of interest

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1323520/full#supplementary-material

References

1. Chang MC. The blind spot and challenges in pain management. *J Yeungnam Med Sci*. (2022) 39:179–80. doi: 10.12701/jyms.2022.00339

2. Lee JH, Chang MC. Some suggestions for pain physicians working in real-world clinical settings. *J Yeungnam Med Sci*. (2023) 40:S123–4. doi: 10.12701/jyms.2023.00255

3. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *MMWR Morb Mortal Wkly Rep*. (2018) 67:1001–6. doi: 10.15585/mmwr.mm6736a2

4. Garland EL. Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways. *Prim Care*. (2012) 39:561–71. doi: 10.1016/j.pop.2012.06.013

5. Sarnthein J, Jeanmonod D. High thalamocortical theta coherence in patients with neurogenic pain. *NeuroImage*. (2008) 39:1910–7. doi: 10.1016/j.neuroimage.2007.10.019

6. Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain*. (2006) 129:55–64. doi: 10.1093/brain/awh631

7. Stern J, Jeanmonod D, Sarnthein J. Persistent EEG overactivation in the cortical pain matrix of neurogenic pain patients. *NeuroImage*. (2006) 31:721–31. doi: 10.1016/j.neuroimage.2005.12.042

8. Walton KD, Dubois M, Llinás RR. Abnormal thalamocortical activity in patients with complex regional pain syndrome (CRPS) type I. *Pain*. (2010) 150:41–51. doi: 10.1016/j.pain.2010.02.023

9. May ES, Hohn VD, Nickel MM, Tiemann L, Gil Ávila C, Heitmann H, et al. Modulating brain rhythms of pain using transcranial alternating current stimulation (tACS)—a sham-controlled study in healthy human participants. *J Pain*. (2021) 22:1256–72. doi: 10.1016/j.jpain.2021.03.150

10. Antal A, Paulus W. Transcranial alternating current stimulation (tACS). *Front Hum Neurosci*. (2013) 7:317. doi: 10.3389/fnhum.2013.00317

11. Elyamany O, Leicht G, Herrmann CS, Mulert C. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. *Eur Arch Psychiatry Clin Neurosci*. (2021) 271:135–56. doi: 10.1007/s00406-020-01209-9

12. Wischnewski M, Alekseichuk I, Opitz A. Neurocognitive, physiological, and biophysical effects of transcranial alternating current stimulation. *Trends Cogn Sci*. (2023) 27:189–205. doi: 10.1016/j.tics.2022.11.013

13. Ahn S, Prim JH, Alexander ML, McCulloch KL, Fröhlich F. Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in patients

with chronic low Back pain: a randomized, crossover, double-blind, sham-controlled pilot study. *J Pain*. (2019) 20:277.e1–277.e11. doi: 10.1016/j.jpain.2018.09.004

14. Antal A, Bischoff R, Stephani C, Czesnik D, Klinker F, Timäus C, et al. Low intensity, transcranial, alternating current stimulation reduces migraine attack burden in a home application set-up: a double-blinded, randomized feasibility study. *Brain Sci*. (2020) 10:888. doi: 10.3390/brainsci10110888

15. Bernardi L, Bertuccelli M, Formaggio E, Rubega M, Bosco G, Tenconi E, et al. Beyond physiotherapy and pharmacological treatment for fibromyalgia syndrome: tailored tACS as a new therapeutic tool. *Eur Arch Psychiatry Clin Neurosci*. (2021) 271:199–210. doi: 10.1007/s00406-020-01214-y

16. Lin AP, Chiu CC, Chen SC, Huang YJ, Lai CH, Kang JH. Using high-definition transcranial alternating current stimulation to treat patients with fibromyalgia: a randomized double-blinded controlled study. *Lifestyles*. (2022) 12:1364. doi: 10.3390/life12091364

17. Prim JH, Ahn S, Davila MI, Alexander ML, McCulloch KL, Fröhlich F. Targeting the autonomic nervous system balance in patients with chronic low Back pain using transcranial alternating current stimulation: a randomized, crossover, double-blind. *J Pain Res*. (2019) 12:3265–77. doi: 10.2147/JPR.S208030

18. Higgins JPT, Green S (2011). Cochrane handbook for systematic reviews of interventions. Version 5.1.0. Available at: http://handbook-5-1.cochrane.org/

19. Arendsen LJ, Henshaw J, Brown CA, Sivan M, Taylor JR, Trujillo-Barreto NJ, et al. Entraining alpha activity using visual stimulation in patients with chronic musculoskeletal pain: a feasibility study. *Front Neurosci*. (2020) 14:828. doi: 10.3389/fnins.2020.00828

20. Babiloni C, Brancucci A, Del Percio C, Capotosto P, Arendt-Nielsen L, Chen AC, et al. Anticipatory electroencephalography alpha rhythm predicts subjective perception of pain intensity. *J Pain*. (2006) 7:709–17. doi: 10.1016/j.jpain.2006.03.005

21. Ploner M, Sorg C, Gross J. Brain rhythms of pain. *Trends Cogn Sci*. (2017) 21:100–10. doi: 10.1016/j.tics.2016.12.001

22. Tu Y, Zhang Z, Tan A, Peng W, Hung YS, Moayedi M, et al. Alpha and gamma oscillation amplitudes synergistically predict the perception of forthcoming nociceptive stimuli. *Hum Brain Mapp*. (2016) 37:501–14. doi: 10.1002/hbm.23048

23. Burgmer M, Gaubitz M, Konrad C, Wrenger M, Hilgart S, Heuft G, et al. Decreased gray matter volumes in the cingulo-frontal cortex and the amygdala in patients with fibromyalgia. *Psychosom Med*. (2009) 71:566–73. doi: 10.1097/PSY.0b013e3181a32da0

24. Staud R, Craggs JG, Perlstein WM, Robinson ME, Price DD. Brain activity associated with slow temporal summation of C-fiber evoked pain in fibromyalgia patients and healthy controls. *Eur J Pain*. (2008) 12:1078–89. doi: 10.1016/j.ejpain.2008.02.002

25. Gücer G, Niedermeyer E, Long DM. Thalamic EEG recordings in patients with chronic pain. *J Neurol*. (1978) 219:47–61. doi: 10.1007/BF00313368

26. Llinás RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci U S A*. (1999) 96:15222–7. doi: 10.1073/pnas.96.26.15222

27. Miyaguchi S, Otsuru N, Kojima S, Yokota H, Saito K, Inukai Y, et al. Gamma tACS over M1 and cerebellar hemisphere improves motor performance in a phase-specific manner. *Neurosci Lett*. (2019) 694:64–8. doi: 10.1016/j.neulet.2018.11.015

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 11 January 2024
DOI 10.3389/fmed.2023.1335405

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OPEN ACCESS

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RECEIVED 15 November 2023
ACCEPTED 19 December 2023
PUBLISHED 11 January 2024

CITATION
Sreckovic S, Ladjevic N, Milicic B, Tulic G, Milovanovic D, Djukanovic M and Kadija M (2024) Chronic post-surgical pain after knee arthroplasty: a role of peripheral nerve blocks.
Front. Med. 10:1335405.
doi: 10.3389/fmed.2023.1335405

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Chronic post-surgical pain after knee arthroplasty: a role of peripheral nerve blocks

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Introduction: Peripheral nerve blocks are an efficient method of pain control after total knee arthroplasty (TKA), but there is no report of their impact on chronic post-surgical pain (CPSP).

Methods: This prospective observational study aimed to assess adductor canal block (ACB) and IPACK block (blocks vs. no blocks) on opioid consumption, postoperative pain score, chronic post-surgical pain 2 years after TKA.

Results: 166 patients (82 vs. 84) were analyzed. Opioid consumption was less in the group with blocks (9.74 ± 3.87 mg vs. 30.63 ± 11.52 mg) ($p < 0.001$). CPSP was present in 20.24% of patients in the group without blocks and 6.1% of patients with blocks ($p = 0.011$). Predictor variables of CPSP included pain before surgery (cut-off of 5.5), pain at rest (cut-off of 2.35), pain during active movement (cut-off: 2.5), and opioid consumption (cut-off: 8 mg).

Conclusion: Peripheral nerve blocks provide adequate analgesia, significantly decrease opioid consumption, improve functional outcomes, and reduce CPSP 2 years after surgery.

KEYWORDS

peripheral nerve block, chronic pain, adductor canal block, IPACK block, knee arthroplasty

1 Introduction

Total knee arthroplasty (TKA) is a standard surgical procedure in the final stages of osteoarthritis associated with intense postoperative pain, especially in the first 24 h postoperatively and during active joint movements (1, 2). After this procedure, different pain management strategies are suggested to provide adequate analgesia without muscle weakness, to enable early rehabilitation, and to prevent chronic pain (3–6). Adductor canal block (ACB) and infiltration in the space between the popliteal artery and the capsule of the posterior knee (IPACK block) are described as an effective method of pain management in these patients, which significantly leads to a reduction in opioid consumption, pain, and improve knee functioning in the immediate postoperative period (5, 6). However, there is no report of their impact on chronic post-surgical pain (CPSP). CPSP after TKA was experienced in up to 44% of patients, and 15% were in severe pain, affecting the quality of life, causing dissatisfaction, and

becoming one of the reasons for revision surgery (7–9). One of the predictors of CPSP is postoperative pain intensity, mainly provoked by movement (10, 11). Some studies suggest that pain duration is equally significant (3, 4). Various pathophysiological mechanisms, including sensitization at the site of surgery and the spinal and supraspinal levels, are responsible for developing chronic pain (12).

The estimation of outcomes after TKA is very challenging. Implant survival was the most commonly referenced measure of success after knee arthroplasty. Patient-reported outcome measures (PROMs) have been widely used to assess pain and function after TKA (13–16).

This single-center, observational study aimed to assess the impact of ACB and IPACK block on the incidence of CPSP and functional recovery 2 years after TKA.

2 Methods

2.1 Patients and study design

The study was carried out by the principles of the Helsinki Declaration. After approval by the Ethics Committee of the University Clinical Centre of Serbia (No 361/14; No 340/1), and obtaining written informed consent 300 patients were included in the study. All patients underwent elective TKA from January 2018 to April 2020, in the Clinic for orthopedics surgery and traumatology, University Clinical Centre of Serbia.

This study was written following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Inclusion criteria were: primary unilateral TKA, age of 40–90 years, ASA I-III, type of implant (NexGen® Complete Knee Solution, Zimmer Biomet, Indiana, United States), no history of ongoing opioid treatment within 30 days before surgery. Exclusion criteria were: incomplete data, psychological, emotional or neurological conditions that may jeopardize postoperative rehabilitation (drug or alcohol abuse, mental illness, neurological diseases-Parkinson's disease, multiple sclerosis, etc.).

2.2 Intervention

All patients underwent a unilateral cemented TKA without patella resurfacing using a tourniquet, inflated to 100–150 mmHg over systolic blood pressure. Spinal anesthesia was performed using levobupivacaine 0.5% up to 3 mL at the level of the L3-L4. If a patient refused spinal anesthesia or there was its contraindication, general anesthesia was induced with midazolam 0.05 mgkg-1, fentanyl 3mcgkg-1, propofol 1.5–2.0 $mgkg^{-1}$, and cisatracurium 0.2 $mgkg^{-1}$. Anesthesia was maintained with sevoflurane at a minimum alveolar concentration of 1. Postoperatively, multimodal analgesia regime depended on the anesthesiologist's affinity and included: (a) non-opioid analgesics (paracetamol 1 g iv. every 8 hours and ketorolac 30 mg iv. every 8 hours); (b) opioid analgesics (tramadol 100 mg iv., morphine 4–6 mg iv/im/sc, and tapentadol 50–100 mg *per os*) and (c) combination of ACB and IPACK block. This combination of nerve blocks was performed by one anesthesiologist. ACB was performed using a linear probe of 10–12 MHz, 15 mL of 0.33% levobupivacaine (10 mL of 0.5% levobupivacaine and 5 mL of 0.9% sodium chloride) injected lateral to the femoral artery at the midpoint of the adductor canal beneath the sartorius muscle. The IPACK block was performed with a curved (2–5 MHz) transducer positioned over the medial thigh. After visualizing the femoral shaft, popliteal artery, and posterior space of the femoral shaft, 15 mL of 0.33% levobupivacaine was injected.

Patients were divided into two groups based on the administration of peripheral nerve blocks, the first group with blocks(ACB and IPACK block) and the second without blocks.

2.3 Postoperative outcomes

2.3.1 Pain intensity

Pain intensity was measured using the Numerical Rating Scale (NRS), at 1 hour, two, three, four, six, eight, 12 h, 16 h, 20 h, and 24 h postoperatively. NRS is commonly used to assess pain severity at that moment in time using a 0–10 scale, with zero meaning *no pain* and 10 meaning *the worst pain imaginable.* Patients were given an intravenous bolus of morphine as *rescue* analgesia when pain at rest was more than three or more than five when they were moving, breathing deeply, or coughing. Morphine in a dose of 1 mg was given every 10 min until the pain intensity was reduced. NRS estimation was also performed during early rehabilitation, five hours after surgery. It included active movements of the operated leg and full flexion of the knee and foot: I-flexion of the foot; II-partial flexion of the knee; III-full flexion of the knee and foot; IV-raising the leg in full extension and holding it for 10 s. Opioid requirements were measured by converting the 24-h opioid consumption into a standardized morphine milligram equivalent (MME).

2.3.2 Functional outcomes

The patient's opinion about the operative knee and associated problems were assessed by *Knee Injury and Osteoarthritis Outcome Score* (KOOS) 2 years after surgery. The questionnaire includes five subscales: *Symptoms and stiffness* (seven items); *Pain* (nine items); *Function, daily living* (17 items); *Function, sports, and recreational activities* (five items) and *Quality of Life* (four items). All items have calculated as the sum and transformed to a 0–100 scale, with zero representing severe knee problems and 100 representing no knee problems. Scores between 0 and 100 represent the percentage of the total possible score achieved. Assessment of patients' ability to forget about the artificially implanted knee joint in performing daily activities was evaluated by the *Forgotten Joint Score* (FJS) 2 years after surgery. Every question is scored from 1 (never) to 5 (mostly) according to the selected response, and the raw score ranges from 12 to 60. The raw score is linearly transformed to a 0–100 scale and then reversed to obtain the final score (Final score = 100 - ((sum(item01 to item12) - 12)/48*100)). Higher scores indicate that the patient is less aware of artificial joint when performing daily activities.

2.3.3 Postoperative complications

Low molecular weight heparin (LMWH) was administrated 12 h before surgery in all patients. The dose was prophylactic or therapeutic, adjusted to the patient's need, according to the value of anti-Xa, and continued in the next 30 days after surgery. Discharge criteria were good health condition with no wound exudation and the flexion angle of the operative knee >90°. Nausea, vomiting, itching, sleepiness, delayed wound healing, drainage or swelling, deep venous thrombosis, and other cardiovascular, neurovascular, or cerebrovascular complications during hospitalization were recorded. The persistence of CPSP in the operative knee was assessed by pain specialists, according to the

International Classification of Diseases, Eleventh Revision (ICD-11) and intensity was estimated using NRS 2 years after surgery (17).

2.4 Statistical analysis

For normal distribution data testing, the Kolmogorov–Smirnov and Shapiro–Wilk tests were used. Descriptive methods (percent, mean, median, standard deviation (SD)) were used to summarize the data. The Pearson X^2 test; Fisher exact test; Kruskal Wallis test; Wilcoxon rank sum test was used to test differences between groups depending on the nature of the examined parameters. The receiver operating characteristic (ROC) curve methods were applied (AUC ROC-area under the ROC curve according to DeLongs method; likelihood ratio test for AUC ROC; the best cut-off value for these parameters was set as value with maximum sensitivity and specificity) to examine the discriminative potential of factors relevant to the presence/absence of CPSP 2 years after TKA. All tests were two-sided, and statistical significance was considered at $p < 0.05$. The statistical analysis was done with the program R version 3.3.2 (2016-10-31) - "Sincere Pumpkin Patch"; Copyright (C) 2016 The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit) (available: www.r-project.org; downloaded: January 21, 2022).

3 Results

This prospective observational study included 166 patients with complete medical data, followed up 2 years after elective TKA. Ninety-six patients had incomplete data, 31 were lost, and seven died within 24 months of follow-up. Data for 82 patients with blocks (ACB and IPACK block) in the first group and 84 in the second without blocks were analyzed (Figure 1). There was no difference between groups regarding patient characteristics- age, sex, ASA status, BMI, and the type of anesthesia. All patients were in pain for more than 3 months before surgery, but there was no difference between groups in pain intensity and the number of painful joints affected (Table 1). Also, there was no difference between groups in the number of patients in pain and its intensity 1 hour after surgery (Table 2). The group with blocks experienced less pain at rest (1.19 ± 0.73 vs. 3.10 ± 1.08 p<0.001) and at the other time points in the first 24 h (Table 2). Also, there was a statistical difference between groups in pain during coughing and active movements of the operated leg (Table 2). In the group with blocks, 68.29% of patients were in pain during flexion of the foot with an intensity of 1.55, while in the group without blocks, 95.25% had a pain intensity of 3.75. Differences between groups also existed during partial flexion of the knee and full extension of the knee and foot. All patients with blocks could raise the leg in full extension and hold it for 10 s, and only eight patients in the group without blocks could perform the same. Pain intensity during this activity was higher in the group without blocks (2.54 ± 1.16vs 8.62 ± 3.11) (Table 2). In the first 24 h after surgery, in the group with blocks, 23.2% of patients needed opioids.

During this period, opioid consumption was less in this group (9.74 ± 3.87 vs. 30.63 ± 11.52) (Table 3). In the following 24 h, 69 (84.1%) patients in the group with blocks were free of opioids, and without blocks 43 (51.2%) ($p < 0.001$), but without difference in the dose of opioids (Table 3).

Two years after surgery, the KOOS score was statistically different between groups. The higher score was in the group with blocks (92.61 ± 10.85 vs. 81.81 ± 12.28 $p < 0.001$) and in all its subscales (Table 4). FJS 2 years after surgery was significantly higher in the group with blocks (92.52 ± 12.43 vs. 78.72 ± 13.94, $p < 0.001$) (Table 4). In the group with blocks, 91.5% of patients had FJS ≥ 22, while without blocks 59.5% ($p < 0.001$) (Table 4).

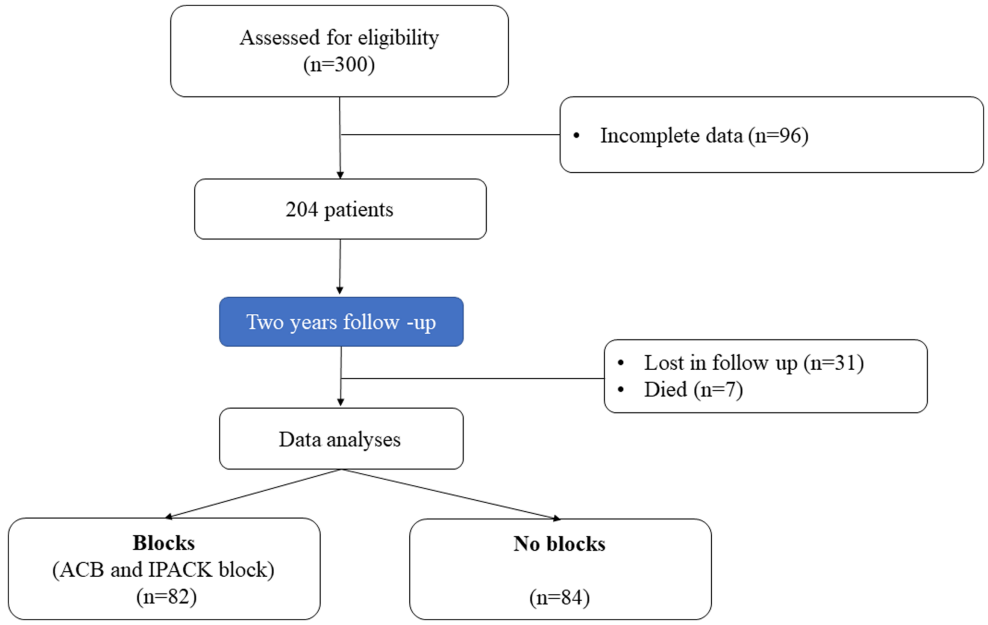

FIGURE 1
Patient selection and study flow.

TABLE 1 Patient characteristics.

Characteristics	Blocks	No blocks	*p* value
Age (y)			
Mean (SD)	68.51 (8.7)	67.14 (7.62)	0.421
Median (range)	68(50–90)	67 (43–90)	
Sex - n (%)			
Male	30 (36.59%)	24 (28.57%)	0.349
Female	52 (63.41%)	60 (71.43%)	
Weight (kg)			
Mean (SD)	84.11 (15.06)	81.19 (13.91)	0.098
Median (range)	85(60–120)	80(56–115)	
Height (m)			
Mean (SD)	1.72 (0.09)	1.71(0.08)	0.346
Median (range)	1.72(1.5–1.91)	1.69(1.52–1.92)	
BMI (kg/m²)			
Mean (SD)	28.32 (3.39)	27.59(3.88)	0.502
Median (range)	28.38(22.23–37.78)	27.47(20.08–38.77)	
ASA physical status - n (%)			
ASA I	1 (1.22%)	1 (1.19%)	0.51
ASA II	38 (46.34%)	46 (54.76%)	
ASA III	43 (52.44%)	37 (44.05%)	
Type of anesthesia - n (%)			
General	31 (37.80%)	26 (30.95%)	0.444
Spinal	51 (62.20%)	58 (69.05%)	
In pain before surgery (during≥3 months)			–
In the knee for surgery	80 (97.6%)	83 (98.8%)	0.983
In the knee & another place	2 (2.4%)	1 (1.2%)	
Pain before surgery (NRS) – mean (SD)	6.11(1.15)	6.33(1.15)	0.21
Total	82 (100%)	84 (100%)	–

BMI-body mass index; ASA- American Society of Anesthesiologists; NRS- Numerical Rating Scale.

In the group without blocks, postoperative complications, nausea ($p < 0.001$), and sleepiness ($p < 0.001$) were more often (Table 5). Vomiting, itching, wound infection, DVT (above and below knee), and pulmonary embolism were not present in either group. One patient had a foot drop in the first group as a complication of performed blocks (Table 5) (18). During 24 months after TKA, there was no readmission to the hospital, and seven patients died in both groups (Table 5). Two years after TKA, CPSP was present in 20.24% of patients in the group without blocks and 6.1% of patients with blocks ($p = 0.011$) without differences in pain intensity (Table 5). Potential predictor variables of CPSP were pain before surgery (cut-off of 5.5), and for the first 24 h after surgery pain at rest (cut-off of 2.35), pain during active movement (cut-off: 2.5), and opioid consumption (cut-off: 8 mg) (Table 6; Figure 2).

4 Discussion

In this study, we assessed opioid consumption, functional outcomes, and CPSP in the case of peripheral nerve blocks and predictor variables of CPSP. Our results suggest that ACB and IPACK block provide adequate analgesia at different time points, significantly reducing opioid consumption and reducing postoperative complications. 23.2% of patients with blocks had needed opioids in the first 24 h with a dose of less than 10 mg. Also, this study showed that this combination of blocks improves functional outcomes by providing higher KOOS and FJS 2 years after surgery. Patients in the group without blocks were more likely to develop CPSP 24 months after TKA. Potential predictor variables of CPSP were pain before surgery (cut-off of 5.5), and for the first 24 h after surgery: pain at rest (cut-off of 2.35), pain during active movement (cut-off: 2.5), and opioid consumption (cut-off: 8 mg).

Peripheral nerve blocks are part of the multimodal analgesia regimen following TKA. ACB is a part of this regimen, preserving quadriceps strength, and enhancing recovery (4, 19, 20). The analgesic efficiency of this block is mainly the result of blocking the saphenous nerve and the nerve to the vastus medialis, which also play a substantial role in knee joint innervation (21). Administering a high volume of a local anesthetic near the end of the adductor canal could unintentionally block other nerves close to the proximal or distal end of the canal (22).

TABLE 2 Postoperative pain score.

Characteristics	In pain – *n* (%)			Pain (NRS) – mean (SD)		
	Blocks	No blocks	*p* value	Blocks	No blocks	*p* value
Pain after surgery, at rest						
1 h	41 (50)	35 (41.67)	0.28	2.34 (1.77)	2.09 (0.74)	0.46
2 h	44 (53.66)	80 (95.24)	<0.001	2.07 (1.23)	2.84 (1.5)	0.004*
3 h	52 (63.41)	84 (100)	<0.001	2 (1.41)	3.54 (1.96)	<0.001
4 h	59 (71.95)	82 (97.62)	<0.001	1.92 (1.25)	3.77 (1.95)	<0.001
6 h	53 (64.63)	80 (95.24)	<0.001	1.53 (0.67)	3.71 (1.92)	<0.001
8 h	54 (65.85)	82 (97.62)	<0.001	1.78 (1.14)	4.02 (1.94)	<0.001
12 h	52 (63.41)	81 (96.43)	<0.001	1.9 (1.5)	4 (1.91)	<0.001
16 h	45 (54.88)	82 (97.62)	<0.001	1.51 (0.79)	3.34 (1.69)	<0.001
20 h	47 (57.32)	81 (96.43)	<0.001	1.51 (0.59)	3.15 (1.57)	<0.001
24 h	47 (57.32)	65 (77.38)	0.006*	1.53 (0.65)	3.4 (1.64)	<0.001
Within 24 h	75 (91.46)	84 (100)	0.006*	1.19 (0.73)	3.10 (1.08)	<0.001
Pain during activity						
Flexion of the foot	56 (68.29)	80 (95.24)	<0.001	1.55 (0.69)	3.75 (1.89)	<0.001
Partial flexion of the knee	58 (70.73)	82 (97.62)	<0.001	1.57 (0.7)	4.2 (1.82)	<0.001
Full flexion of the knee and foot	64 (78.05)	84 (100)	<0.001	1.78 (0.88)	8.77 (2.03)	<0.001
Raising the leg in full extension and holding it for 10 s, done	82 (100)	8 (9.52)	<0.001	2.54 (1.16)	8.62 (3.11)	<0.001
Pain during coughing						
In pain	5 (6.1)	55 (65.48)	<0.001	1.6 (0.55)	3.75 (1.54)	0.001*
Total	82 (100)	84 (100)	-	82 (100)	84 (100)	-

NRS- Numerical Rating Scale; *$p < 0.05$.

TABLE 3 Postoperative opioid consumption.

Characteristics	Patients who needed opioids – N (%)			Dose of opioids (mg) – mean (SD)		
	Blocks	No blocks	p value	Blocks	No blocks	*p* value
Opioids consumption						
Within 24 h	19 (23.17%)	84 (100%)	<0.001	9.74 (3.87)	30.63 (11.52)	<0.001
24-48 h	13 (15.85%)	41 (48.81%)	<0.001	11.62 (5.38)	13.9 (4.94)	0.189
48 h-72 h	2 (2.44%)	1 (1.19%)	0.983	10 (0)	20 (0)	0.496
Total	82 (100%)	84 (100%)	–	82 (100%)	84 (100%)	–

But continuous ACB does not have the benefit of single-shot ACB (23). Zhang et al., showed that ACBs do not provide better pain control than LIA (75 mL total volume included 150mg of ropivacaine, 30mg of ketorolac, adrenaline 200μg and 10mg of morphine), while their combination had been recommended after TKA (24). Pain occurring in the posterior and lateral aspects of the knee after TKA is not covered by the ACB. A new ultrasound-guided technique has been devised that comprises infiltration of the local anesthetic between the popliteal artery and capsule of the posterior knee and provides effective analgesia to the posterior aspect of the knee without affecting muscle strength (25). Combining ACB with IPACK block provides adequate analgesia to the anterior and posterior aspects of the knee without affecting muscle strength (5, 6, 26). In the meta-analysis, Hussain et al. reported that in the absence of LIA, adding IPACK to ACB reduces pain for up to 24 h, enhances functional recovery, and does not support the addition of IPACK to ACB when LIA is routinely administered (27). However, for opioid-sparing effects and for pain scores different minimally clinically important difference (MCIDs) has been used in most studies (28). Laigaard et al. concluded that median clinician-perceived MCIDs in postoperative pain management were 10 mg iv morphine equivalents or 40% of opioid consumption and 15-18 mm or 30% for pain scores (28). Different analgesia regimens enable most patients to be at low risk for moderate or severe pain (29). The use of rescue analgesics for a minor reduction in pain scores and opioid consumption has been dampening, and the patients with higher baseline pain scores may be more responsible for treatment effects (29). Our study showed that if ACB and

TABLE 4 KOOS and FJS 2 years after knee arthroplasty.

Characteristics, 2 years after surgery	Blocks	No blocks	*p* value
KOOS (%)			
Mean (SD)	92.61 (10.85)	81.81 (12.28)	<0.001
Median (Range)	94.5 (38–100)	83.5 (38–100)	
Symptoms + Stiffness (%)			
Mean (SD)	92.83 (12.14)	84.13 (14.63)	<0.001
Median (Range)	96 (25–100)	89 (8–100)	
Pain (%)			
Mean (SD)	93.77 (10.19)	74.19 (14.87)	<0.001
Median (Range)	97 (28–100)	78 (25–100)	
Function, daily living (%)			
Mean (SD)	92 (11.46)	81.88 (14.05)	<0.001
Median (Range)	94 (35–100)	85 (25–100)	
Function, sports, and recreational activities (%)			
Mean (SD)	91.38 (11.87)	79.1 (13.27)	<0.001
Median (Range)	95 (35–100)	80 (30–100)	
Quality of life (%)			
Mean (SD)	96.26 (10.23)	88.9 (11.65)	<0.001
Median (Range)	100 (31–100)	91 (44–100)	
FJS total (%)			
Mean (SD)	92.52 (12.43)	78.72 (13.94)	<0.001
Median (Range)	95.83 (33.33–100)	81.25(29.17–97.92)	
FJS categories – N (%)			
FJS ≥ 22	75 (91.5%)	50 (59.5%)	<0.001
FJS < 22	7 (8.5%)	34 (40.5%)	
Total	82 (100%)	84 (100%)	–

KOOS- Knee Injury and Osteoarthritis Outcome Score; FJS- Forgotten Joint Score.

TABLE 5 Postoperative complications.

Characteristics	Blocks	No blocks	*p*-value
Postoperative complications			
Chronic post-surgical pain			
Presence-*n* (%)	5 (6.1%)	17 (20.24%)	0.007*
Pain- NRS			
Mean (SD)	3.8 (0.45)	3.65 (0.61)	0.18
Median (Range)	4 (3–4)	4 (3–5)	
Nausea, n (%)	0 (0%)	24 (28.6%)	<0.001
Sleepiness, n (%)	4 (4.88%)	49 (58.33%)	<0.001
Foot drop, n (%)	1 (1.22%)	0 (0%)	0.309
Wound drainage, n (%)	1 (1.22%)	1 (1.19%)	0.986
Urinary tract infection, n (%)	2 (2.44%)	3 (3.57%)	0.669
Characteristics, 2 years after surgery			
24-month mortality, n (%)	3 (3.66%)	4 (4.76%)	0.724
Total, n(%)	82 (100%)	84 (100%)	–

NRS- Numerical Rating Scale; *- $p < 0.05$.

IPACK block were applied, some patients were not in pain, and for those who needed opioids, the dose was less than 10 mg iv in the first 24 h postoperatively. Between our groups during the first hour postoperatively, there were not any differences, which can be explained by the duration of spinal anesthesia or good analgesia during general anesthesia. Nausea and sleepiness, as opioid-induced side effects, were in the group without blocks as effects of higher opioid postoperative consumption.

Estimation of the outcome after TKA changes through time. Improvements in surgical techniques and implant design made patient satisfaction evolving the most referenced measure of success (30, 31). However, approximately 20% of patients after TKA are dissatisfied with the outcome, and up to 34%, experienced moderate to severe pain 3 months after surgery (32, 33). CPSP is the most common cause of dissatisfaction and one of the reasons for revision surgery after TKA (32). Sakellariou et al. showed that 39 % of patients had persistent pain ranging from 3–5 out of 10 a year after TKA (33). While Lui et al. included 1,030 patients after TKA and showed that the rate of persistent pain after TKA was 53% 1 year after surgery (34). Our study showed that 2 years after TKA, CPSP was present in 6% of patients with ACB and IPACK blocks and 20% of patients without blocks without difference in pain intensity. Various factors have been identified as predictive factors of CPSP. Several single gene mutations have been identified as potential risk factors for increased sensitivity but without powerful predictive value for CPSP. Biological characteristics usually include age and sex, where younger adults and female sex patients are more prone to developing CPSP. Also, patients with increased BMI and persistent comorbidities are at greater risk (28–35). Psychological factors that could have a greater impact on the development of CPSP include depression, sleep disorders, fear of undergoing surgery, anxiety, and a tendency to exaggerate surgery outcomes. Socioeconomic factors usually include lower education levels, marital status, where unmarried patients are at greater risk, smoking, and unemployment (35–42).

Preoperative pain scores and more severe acute postoperative pain were associated with a higher risk of CPSP after TKA (10, 11, 43). Our study showed that risk factors for CPSP are: pain before surgery (higher 5.5 NRS), pain at rest (higher than 2.35 NRS), and during active movement (higher than 2.5 NRS), and opioid consumption of 8 mg. Although there is little evidence of the type and impact of perioperative interventions that reduce CPSP, our results imply the importance of perioperative pain control on the occurrence of CPSP.

KOOS score in the group without blocks was mainly affected by pain. FJS, a newer and more sensitive score, registers the differences in the functioning of more active patients after TKA. Recently, Clement et al. reported that a postoperative FJS of 22 or more, was predictive of achieving a patient-acceptable symptom state (44). Our study showed that the group with ACB and IPACK blocks had 91.5%

TABLE 6 Results of the ROC analysis.

Characteristics	Area Under the ROC curve		ROC cut-off value[c]		
	AUC ROC[a] (95%CI)	Likelihood ratio test[b]	Cut-off value	Sensitivity (95% CI)	Specifity (95% CI)
Pain before surgery (NRS)	65.23 (53.72–76.74)	0.0155*	5.5	34.72 (27.08–43.06)	86.36 (72.73–100)
During the first 24 h after surgery					
Pain at rest (NRS)	70.57 (60.74–80.39)	0.002*	2.35	72.73 (54.55–90.91)	61.81 (54.17–70.14)
Pain during flexion of the foot (NRS)	63.21 (51.3–75.12)	0.105	–	–	–
Pain during partial flexion of the knee (NRS)	63.59 (52.16–75.02)	0.131	–	–	–
Pain during full flexion of the knee and foot (NRS)	63.54 (52.24–74.84)	0.045*	2.5	81.82 (63.64–95.45)	47.22 (39.58–55.56)
Opioid consumption during the first 24 h (mg)	64.63 (52.82–76.44)	0.032*	8	81.82 (63.64–95.45)	43.75 (35.42–52.08)

[a]Area Under the ROC curve (DeLong's method).
[b]Likelihood ratio test for AUC ROC.
[c]Value with maximum sensitivity and specificity; NRS- Numerical Rating Scale; * $p<0.05$.

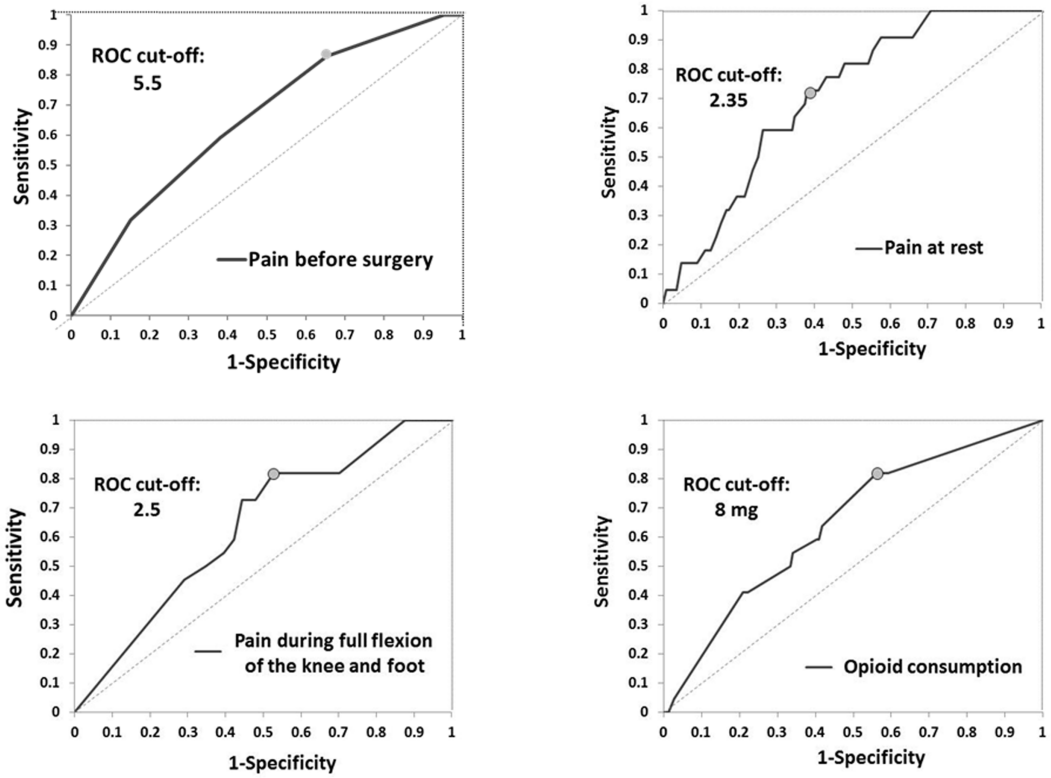

FIGURE 2
ROC curves.

of patients with FJS ≥ 22, while in the group without blocks, there were only 59.5% ($p < 0.001$).

The limitations of our study include the fact that this was a single-center design. Also, we did not have preoperative values for KOOS and FJS and estimation of psychological factors such as expected pain, depression, sleep disorders, fear of undergoing surgery, anxiety, and a tendency to exaggerate surgery outcomes that could influence recovery and CPSP. The patients in the study group did not have a uniform rehabilitation program, which could also affect our results. Our study provides a basis for further validation in randomized control studies.

5 Conclusion

The combination of ACB and IPACK block provides adequate analgesia at various time points postoperatively, enabling early rehabilitation, significantly decreasing opioid consumption, improving functional outcomes by providing higher KOOS and FJS and reducing CPSP 2 years after surgery. Pain intensity before surgery at less than 5.5, at rest at less than 2.35, pain during active movement at 2.5, and opioid consumption at less than 8 mg reduce the incidence of CPSP. Randomized controlled trials with long-term follow-up are

needed to confirm the beneficial effects of ACB and IPACK block after TKA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of University Clinical Centre of Serbia. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. NL: Conceptualization, Supervision, Validation, Writing – review & editing. BM: Data curation, Methodology, Software, Writing – review & editing. GT: Conceptualization, Supervision, Writing – review & editing. DM: Investigation, Methodology, Validation, Writing – original draft. MD: Data curation, Investigation, Writing – original draft. MK: Conceptualization, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Rasmussen S, et al. Total knee replacement and non-surgical treatment of knee osteoarthritis: 2-year outcome from two parallel randomized controlled trials. *Osteoarthr Cartil*. (2018) 26:1170–80. doi: 10.1016/j.joca.2018.04.014

2. American Academy of Orthopaedic Surgeons. (n.d.) *Surgical Management of Osteoarthritis of the knee evidence based clinical practice guideline*. Available at: http://www.aaos.org/smoak2cpg

3. Lavand'homme PM, Kehlet H, Rawal N, Joshi GP. PROSPECT working Group of the European Society of regional anaesthesia and pain therapy (ESRA). Pain management after total knee arthroplasty: procedure specific postoperative pain management recommendations. *Eur J Anaesthesiol*. (2022) 39:743–57. doi: 10.1097/EJA.0000000000001691

4. Karpetas GZ, Spyraki MK, Giakoumakis SI, Fligou FG, Megas PD, Voyagis GS, et al. Multimodal analgesia protocol for pain management after total knee arthroplasty: comparison of three different regional analgesic techniques. *J Musculoskelet Neuronal Interact*. (2021) 21:104–12.

5. Mou P, Wang D, Tang XM, Zeng WN, Zeng Y, Yang J, et al. Adductor Canal block combined with IPACK block for postoperative analgesia and function recovery following Total knee arthroplasty: a prospective, double-blind, randomized controlled study. *J Arthroplast*. (2022) 37:259–66. doi: 10.1016/j.arth.2021.10.004

6. Eccles CJ, Swiergosz AM, Smith AF, Bhimani SJ, Smith LS, Malkani AL. Decreased opioid consumption and length of stay using an IPACK and Adductor Canal nerve block following Total knee arthroplasty. *J Knee Surg*. (2021) 34:705–11. doi: 10.1055/s-0039-1700840

7. Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, et al. Chronic postsurgical pain in Europe: an observational study. *Eur J Anaesthesiol*. (2015) 32:725–34. doi: 10.1097/EJA.0000000000000319

8. Gungor S, Fields K, Aiyer R, Valle AGD, Su EP. Incidence and risk factors for development of persistent postsurgical pain following total knee arthroplasty: a retrospective cohort study. *Medicine (Baltimore)*. (2019) 98:e16450. doi: 10.1097/MD.0000000000016450

9. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain - update on incidence, risk factors and preventive treatment options. *BJA Educ*. (2022) 22:190–6. doi: 10.1016/j.bjae.2021.11.008

10. Rice DA, Kluger MT, McNair PJ, Lewis GN, Somogyi AA, Borotkanics R, et al. Persistent postoperative pain after total knee arthroplasty: a prospective cohort study of potential risk factors. *Br J Anaesth*. (2018) 121:804–12. doi: 10.1016/j.bja.2018.05.070

11. Lavand'homme PM, Grosu I, France MN, Thienpont E. Pain trajectories identify patients at risk of persistent pain after knee arthroplasty: an observational study. *Clin Orthop Relat Res*. (2014) 472:1409–15. doi: 10.1007/s11999-013-3389-5

12. Lavand'homme P. Transition from acute to chronic pain after surgery. *Pain*. (2017) 158:S50–4. doi: 10.1097/j.pain.0000000000000809

13. Orr MNKlika AK, Emara AK, Piuzzi NS, Higuera-Rueda CA, Barsoum WK, et al. Combinations of preoperative patient-reported outcome measure phenotype (pain, function, and mental health) predict outcome after Total knee arthroplasty. *J Arthroplast*. (2022) 37:S110–S120.e5. doi: 10.1016/j.arth.2022.02.090

14. Canovas F, Dagneaux L. Quality of life after total knee arthroplasty. *Orthop Traumatol Surg Res*. (2018) 104:S41–6. doi: 10.1016/j.otsr.2017.04.017

15. Halawi MJ, Jongbloed W, Baron S, Savoy L, Williams VJ, Cote MP. Patient dissatisfaction after primary Total joint arthroplasty: the patient perspective. *J Arthroplast*. (2019) 34:1093–6. doi: 10.1016/j.arth.2019.01.075

16. Khan M, Osman K, Green G, Haddad F. The epidemiology of failure in total knee arthroplasty. *Bone Joint J*. (2016) 98-B:105–12. doi: 10.1302/0301-620X.98B1.36293

17. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. *Pain*. (2019) 160:45–52. doi: 10.1097/j.pain.0000000000001413

18. Sreckovic SD, Tulic GDZ, Jokanovic MN, Dabetic UDJ, Kadija MV. Delayed foot drop after a combination of the adductor canal block and IPACK block following total knee arthroplasty. *J Clin Anesth*. (2021) 73:110363. doi: 10.1016/j.jclinane.2021.110363

19. Wang CG, Ding YL, Wang YY, Liu JY, Zhang Q. Comparison of adductor canal block and femoral triangle block for total knee arthroplasty. *Clin J Pain*. (2020) 36:558–61. doi: 10.1097/AJP.0000000000000833

20. Summers S, Mohile N, McNamara C, Osman B, Gebhard R, Hernandez VH. Analgesia in Total knee arthroplasty: current pain control modalities and outcomes. *J Bone Joint Surg Am*. (2020) 102:719–27. doi: 10.2106/JBJS.19.01035

21. Laurant DBS, Peng P, Arango LG, Niazi AU, Chan VW, Agur A, et al. The nerves of the Adductor Canal and the innervation of the knee. *Reg Anesth Pain Med*. (2016) 41:321–7. doi: 10.1097/AAP.0000000000000389

22. Tran J, Chan VWS, Peng PWH, Agur AMR. Evaluation of the proximal adductor canal block injectate spread: a cadaveric study. *Reg Anesth Pain Med*. (2019) 45:124–30. doi: 10.1136/rapm-2019-101091

23. Elkassabany NM, Cai LF, Badiola I, Kase B, Liu J, Hughes C, et al. A prospective randomized open-label study of single injection versus continuous adductor canal block

for postoperative analgesia after total knee arthroplasty. *Bone Joint J.* (2019) 101-B:340–7. doi: 10.1302/0301-620X.101B3.BJJ-2018-0852.R2

24. Zhang Q, Fan L. Comparison adductor canal block combined with local infiltration analgesia and adductor canal block alone for pain management after total knee arthroplasty: a randomized controlled trial protocol. *Medicine (Baltimore)*. (2020) 99:e21881. doi: 10.1097/MD.0000000000021881

25. Niesen AD, Harris DJ, Johnson CS, Stoike DE, Smith HM, Jacob AK, et al. Interspace between popliteal artery and posterior capsule of the knee (IPACK) Injectate spread: a cadaver study. *J Ultrasound Med*. (2019) 38:741–5. doi: 10.1002/jum.14761

26. Zheng FY, Liu YB, Huang H, Xu S, Ma XJ, Liu YZ, et al. The impact of IPACK combined with adductor canal block under ultrasound guidance on early motor function after total knee arthroplasty. *Braz J Anesthesiol*. (2022) 72:110–4. doi: 10.1016/j.bjane.2021.04.012

27. Hussain N, Brull R, Sheehy B, Dasu M, Weaver T, Abdallah FW. Does the addition of iPACK to adductor canal block in the presence or absence of periarticular local anesthetic infiltration improve analgesic and functional outcomes following total knee arthroplasty? A systematic review and meta-analysis. *Reg Anesth Pain Med*. (2021) 46:713–21. doi: 10.1136/rapm-2021-102705

28. Laigaard J, Pedersen C, Rønsbo TN, Mathiesen O, Karlsen APH. Minimal clinically important differences in randomised clinical trials on pain management after total hip and knee arthroplasty: a systematic review. *Br J Anaesth*. (2021) 126:1029–37. doi: 10.1016/j.bja.2021.01.021

29. Myles S, Myles B. Conflating effect size and minimal clinically important difference. *Br J Anaesth*. (2021) 126:1029–37. doi: 10.1016/j.bja.2021.09.018

30. Bourne R, Chesworth B, Davis A, Mahomed N, Charron K. Patient satisfaction after total knee arthroplasty: who is satisfied and who is not? *Clin Orthop Relat Res*. (2010) 468:57–63. doi: 10.1007/s11999-009-1119-9

31. Scott CEH, Howie CR, MacDonald D, Biant LC. Predicting dissatisfaction following total knee replacement: a prospective study of 1217 patients. *J Bone Joint Surg*. (2010) 92:1253–8. doi: 10.1302/0301-620X.92B9.24394

32. Irmola T, Ponkilainen V, Mäkelä KT, Robertsson O, W-Dahl A, Furnes O, et al. Impact of Nordic arthroplasty register association (NARA) collaboration on demographics, methods and revision rates in knee arthroplasty: a register-based study from NARA 2000-2017. *Acta Orthop*. (2022) 93:866–73. doi: 10.2340/17453674.2022.5256

33. Sakellariou VI, Poultsides LA, Ma Y, Bae J, Liu S, Sculco TP. Risk assessment for chronic pain and patient satisfaction after total knee arthroplasty. *Orthopedics*. (2016) 39:55–62. doi: 10.3928/01477447-20151228-06

34. Liu SS, Buvanendran A, Rathmell JP, Sawhney M, Bae JJ, Moric M, et al. A crosssectional survey on prevalence and risk factors for persistent postsurgical pain 1 year after total hip and knee replacement. *Reg Anesth Pain Med*. (2012) 37:415–22. doi: 10.1097/AAP.0b013e318251b688

35. Lindberg MF, Miaskowski C, Rustøen T, Cooper BA, Aamodt A, Lerdal A. Preoperative risk factors associated with chronic pain profiles following total knee arthroplasty. *Eur J Pain*. (2021) 25:680–92. doi: 10.1002/ejp.1703

36. Hasegawa M, Tone S, Naito Y, Sudo A. Preoperative pain catastrophizing affects pain outcome after total knee arthroplasty. *J Orthop Sci*. (2022) 27:1096–9. doi: 10.1016/j.jos.2021.05.011

37. Sideris A, Malahias MA, Birch G, Zhong H, Rotundo V, Like BJ, et al. Identification of biological risk factors for persistent postoperative pain after total knee arthroplasty. *Reg Anesth Pain Med*. (2022) 47:161–6. doi: 10.1136/rapm-2021-102953

38. Springborg AH, Visby L, Kehlet H, Foss NB. Psychological predictors of acute postoperative pain after total knee and hip arthroplasty: a systematic review. *Acta Anaesthesiol Scand*. (2023) 67:1322–37. doi: 10.1111/aas.14301

39. George SZ, Bolognesi MP, Bhavsar NA, Penrose CT, Horn ME. Chronic pain prevalence and factors associated with high impact chronic pain following Total joint arthroplasty: an observational study. *J Pain*. (2022) 23:450–8. doi: 10.1016/j.jpain.2021.09.007

40. Tang S, Jin Y, Hou Y, Wang W, Zhang J, Zhu W, et al. Predictors of chronic pain in elderly patients undergoing Total knee and hip arthroplasty: a prospective observational study. *J Arthroplast*. (2023) 38:1693–9. doi: 10.1016/j.arth.2023.04.055

41. Lo LWT, Suh J, Chen JY, Liow MHL, Allen JC, Lo NN, et al. Early postoperative pain after Total knee arthroplasty is associated with subsequent poorer functional outcomes and lower satisfaction. *J Arthroplast*. (2021) 36:2466–72. doi: 10.1016/j.arth.2021.02.044

42. Ashoorion V, Sadeghirad B, Wang L, Noori A, Abdar M, Kim Y, et al. Predictors of persistent post-surgical pain following Total knee arthroplasty: a systematic review and meta-analysis of observational studies. *Pain Med*. (2023) 24:369–81. doi: 10.1093/pm/pnac154

43. Ghoshal A, Bhanvadia S, Singh S, Yaeger L, Haroutounian S. Factors associated with persistent postsurgical pain after total knee or hip joint replacement: a systematic review and meta-analysis. *Pain Rep*. (2023) 8:e1052. doi: 10.1097/PR9.0000000000001052

44. Clement ND, Scott CEH, Hamilton DF, MacDonald D, Howie CR. Meaningful values in the forgotten joint score after total knee arthroplasty. *Bone Joint J*. (2021) 103-B:846–54. doi: 10.1302/0301-620X.103B5.BJJ-2020-0396.R1

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 16 January 2024
DOI 10.3389/fmed.2023.1337711

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RECEIVED 13 November 2023
ACCEPTED 30 December 2023
PUBLISHED 16 January 2024

CITATION
Escobar-Sánchez I, Ríos -León M and Taylor J (2024) Long-term bilateral change in pain and sensitivity to high-frequency cutaneous electrical stimulation in healthy subjects depends on stimulus modality: a dermatomal examination.
Front. Med. 10:1337711.
doi: 10.3389/fmed.2023.1337711

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Long-term bilateral change in pain and sensitivity to high-frequency cutaneous electrical stimulation in healthy subjects depends on stimulus modality: a dermatomal examination

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Introduction: Contradictory changes in pain and sensitivity at long-term following cutaneous 100 Hz high frequency stimulation (HFS) have been previously observed. Thus, we aimed to document long-lasting changes in multimodal sensitivity following HFS, and factors influencing them.

Methods: Long-lasting changes were assessed with mechanical [brush, von Frey filament (588.2 mN)] and thermal [heat (40°C)/cold (25°C)] bedside sensory testing, and electrical TS (0.2 ms single electrical stimuli), at the homotopic (ipsilateral C6 dermatome), adjacent heterotopic (ipsilateral C5 and C7 dermatomes) and contralateral (contralateral C6 dermatomes) dermatomal sites in a single testing session. TS were applied before and after application of 100 Hz HFS at the ipsilateral C6 dermatome. Subjects rated their sensation and pain intensity to TS, and completed questionnaires related to pain descriptors and quality of life.

Results: Long-lasting changes in mechanical and cold sensitivity was detected up to 45 min after HFS at homotopic C6 dermatome, and a temporary increase in cold sensitivity at 20 min in the contralateral C6 dermatome ($p < 0.05$). A slow development of bilateral depotentiation to electrical pain TS was also detected from 40 min after HFS ($p < 0.05$). Higher HFS-induced mechanical and cold sensitivity was identified in women ($p < 0.05$). Age and quality of life were associated with pain intensity ($p < 0.05$).

Conclusion: Long-term unilateral and bilateral changes in sensation and pain following electrical HFS have been found. These findings may suggest a new insight into the development of persistent pain mechanisms. Further studies are now needed.

KEYWORDS

high-frequency stimulation, long-term potentiation, nociception, pain, sensitivity

1 Introduction

Cutaneous electrical high-frequency stimulation (HFS) induces long-term potentiation (LTP), a neural mechanism of synaptic plasticity that contributes to long-lasting experimental allodynia and hyperalgesia following sensitization of spinal nociceptive pathways (1–5). Indeed, the further study of LTP in patients with clearly defined peripheral or central nervous system injury could lead to a better understanding of the time course and pathophysiology of changes in nociception, and the development of new strategies for the prevention and treatment in acute and chronic pain pathologies (1, 2). More recently widespread changes in nociception and pain have been characterized in patients with unilateral neuropathic pain, including adjacent and contralateral testing sites (6, 7). Information is now required to document rapid changes in multimodal sensitivity at several test dermatomes following cutaneous electrical HFS during the changes in nociception and experimental pain.

LTP-like pain amplification (pain-LTP) has been reported following cutaneous electrical HFS at stimulus intensities sufficient to activate C-fiber nociceptors (2, 3, 8). Indeed, the use of electrode with small contact areas favors the activation of superficial nociceptive Aδ fiber and C fiber (3). Although increased pain intensity has been demonstrated with electrical stimuli applied within the homotopic HFS area (3, 9), reduction in electrical pain perception has also been reported (5, 9–11).

Change in pain sensitivity was also observed outside the HFS site (heterotopic hyperalgesia) as assessed with mechanical pinprick stimuli (1, 3, 11–14). Furthermore, a long-lasting heterotopic increase in painful sensations in response to dynamic mechanical tactile stimuli (3, 10, 13) and heat stimuli were also observed (15). However, other studies have shown that thermal sensitivity remained unaltered after HFS (14). These findings support the hypothesis that homosynaptic and heterosynaptic mechanisms related to LTP could play a role in the development of primary and secondary hyperalgesia (9, 16–18), leading to peripheral and central sensitization to multimodal stimuli in the same and adjacent dermatomes. Finally, HFS-induced pain-LTP responses may also be affected by demographic or psychological factors (13, 19, 20) which may modulate the perception of experimental pain.

The aim of this study was to document long-lasting changes in mechanical, thermal, and electrical test stimuli at adjacent homotopic and heterotopic dermatomal sites following cutaneous electrical HFS, and to identify the impact of demographic and clinical factors on induced experimental pain.

2 Materials and methods

This study protocol was approved by the local Clinical Research Ethics Committee (Approval number 149; 2022) and conducted according to the Declaration of Helsinki (21). Participants were recruited from a reference national hospital in Toledo (Spain). All individuals provided written informed consent before their inclusion in the study.

2.1 Subjects

Twelve participants aged between 18 and 80 years were recruited (50% women, mean age = 31 ± 15; Table 1). The exclusion criteria were history of chronic pain or/and neurological or psychiatric diseases, peripheral nervous system injury or neuropathy, diseases causing potential neural damage (e.g., diabetes, diseases of the immune system, oncological diseases), previous clinical history of cervical surgery, injuries or surgery affecting the upper limb, altered sensitivity in the tested regions, frequent headaches, and/or orofacial pain.

2.2 Experimental protocol

Each subject was invited to participate in a single testing session that lasted approximately 1 h. Sensory testing was conducted in a quiet indoor laboratory at ambient temperature (22°C–26°C). The subjects sat in a comfortable chair and were familiarized with the experimental procedure. Participants were prohibited from undertaking vigorous physical activities or drinking caffeinated beverages at least 24 h before the experiment.

The session started with baseline testing with stimuli (TS, see below) applied at the C5, C6, and C7 dermatomes at the dominant side, and at the contralateral C6 dermatome at 5 min intervals for 15 min (see Figure 1 and TS section below). The cutaneous electrical HFS was then applied to the C6 dermatome at the dominant side during 60 s (see HFS section below), and the subject was asked to rate the electrical pain intensity during the electrical stimulus. After HFS, TS were applied to the C5, C6, and C7 dermatomes at the dominant side, and at the contralateral C6 dermatome to detect homotopic and heterotopic effects at 5 min intervals for 45 min. Thus, the study compared post HFS effects on sensory and pain intensity with the 15 min baseline recordings made from the same participant. Subjects were blinded to the study hypothesis.

2.2.1 High frequency stimulation (HFS)

Electrical stimuli were applied through a bipolar concentric electrode (522100, BCS-probe 90 mm straight, Inomed Medizintechnik GmbH, Emmendingen, Germany; diameter, 2 mm) on the dominant forearm, 5 cm distal to the cubital fossa (C6 dermatome) at the dominant side (conditioned site, Figure 1), using a constant current stimulator (DS7A, Digitimer Ltd., Hertfordshire, United Kingdom) (1, 3). The small diameter of the electrode permitted delivery of a high current density achieved at low stimulus intensities, which favors activation of superficial nociceptive Aδ fiber and C fiber afferents (3). Stimulus intensity was adjusted at which the electrical stimulus induced a pain rating of 4/10 ("Pain-4") for each participant with the 11-point numerical rating scale (NRS; 0: no pain, 10: maximum pain) (22): prior to electrical TS and CS, "Pain-4" was assessed and determined by applying single electrical pulses (see below). In this sample, intensity for "Pain-4" corresponded to 10 times the electrical detection threshold (DTh) (1–4, 10, 13, 14, 23, 24) (mean intensity: 1.2 ± 0.8 mA).

The cutaneous electrical HFS was applied as a 1 s train of five pulses applied at 100 Hz (2 ms pulse width), repeated every 10 s inter-train intervals for 1 min, to induce pain-LTP (1, 3). The participants reported the HFS pain intensity with the NRS (0: no pain; 10: maximum pain) at 10 s intervals.

If the perceived pain became unbearable, subjects were allowed to remove their arm from the stimulating electrode at any time.

2.2.2 Test stimuli (TS)

Changes in sensory and pain sensitivity were tested using three different test stimuli (TS): electrical, mechanical, and thermal TS. The

TABLE 1 Baseline demographic and clinical characteristics of healthy participants ($n = 12$).

Subject number	Sex	Age (years)	BMI	EQ-5D-5L (VAS)	EQ-5D-5L (index)	PHQ-9	GAD-7
#1	M	57	32.1	90	1	0	2
#2	M	24	27.3	95	1	11	5
#3	F	43	19.9	70	1	6	4
#4	F	20	21.3	95	1	2	1
#5	F	22	26.0	95	1	5	9
#6	F	30	22.3	95	0.80	4	10
#7	F	21	23.3	80	1	4	5
#8	M	30	23.4	100	1	3	0
#9	M	21	21.1	95	1	4	1
#10	M	22	23.3	95	1	4	1
#11	F	63	17.0	95	0.80	0	1
#12	M	19	25.3	70	0.74	5	7
Total ($n = 12$)	6 M 6F	31 ± 15.1	23.6 ± 3.9	89.6 ± 10.3	0.94 ± 0.1	4 ± 2.9	3.8 ± 3.4

BMI, body mass index; EQ-5D-5L, the five-level version of EuroQol-5D; F, female; GAD-7, the 7-item generalized anxiety disorder (GAD) scale; M, male; PHQ-9, the Patient Health Questionnaire-9; VAS, visual analogue scale.

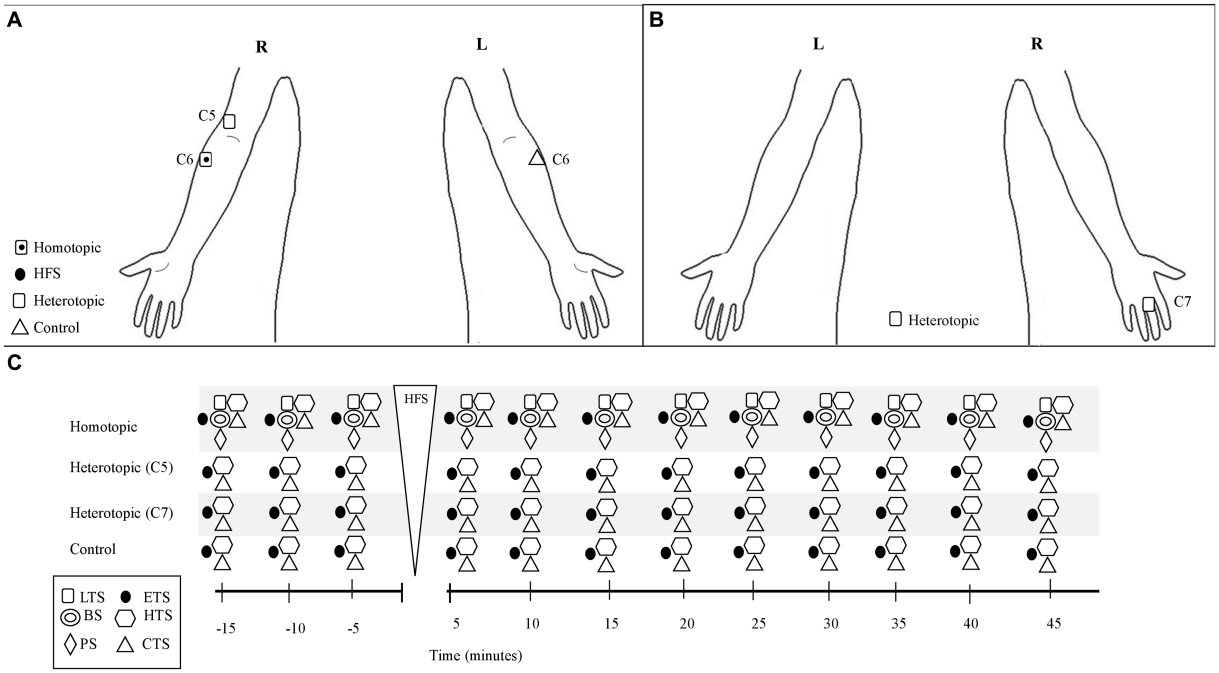

FIGURE 1
Schematic of the 100 Hz-HFS experimental test protocol and stimulation location of the test and conditioning stimuli. **(A)** Frontal plane (anterior): anatomical locations for application of the test stimuli and conditioning stimulus (HFS). **(B)** Frontal plane (posterior): anatomical locations for the test stimuli. **(C)** Schematic of the experimental protocol. The test stimuli were applied at 5 min intervals before and up to 45 min after the electrical HFS, which was applied for 60 s at the C6 dermatome on the dominant arm. Test stimuli were applied at the C6 (homotopic), C5, and C7 (heterotopic) dermatomes on the dominant arm, and at the contralateral C6 dermatome at 5 min intervals. BS, brush stimulus; CTS, cold test stimulus; ETS, electrical test stimulus; HTS, heat test stimulus; LTS, light touch stimulus; PS, pinprick stimulus; R, right; L, left.

TS were applied at the forearm 5 cm distal to the cubital fossa corresponding to the C6 dermatome (3) at the dominant (homotopic site) and nondominant (contralateral C6 dermatome, control site) sides (Figure 1). At the dominant side, TS were also applied to the lateral (radial) side of the antecubital fossa just proximal to the elbow and dorsal surface of the proximal phalanx of the middle finger corresponding to the C5 and C7 dermatomes (heterotopic sites, Figure 1), respectively, according to the American Spinal Injury

Association Impairment Scale Key Sensory Point (25). These TS sites were selected to identify local spinal modulatory effects following the HFS.

2.2.2.1 Electrical TS

Electrical TS were applied with the bipolar concentric electrode (522100, BCS-probe 90 mm straight, Inomed Medizintechnik GmbH, Emmendingen, Germany; 2 mm tip diameter) applied over the selected dermatomal test sites with a constant current stimulator (DS7A, Digitimer Ltd., Hertfordshire, United Kingdom) (3). The electrical TS was presented as 3 pulses (2 ms pulse width) applied at 0.2 Hz for repeated at 5 min intervals during 15 min prior to HFS. The electrical TS were applied at "Pain-4" intensity as assessed previously for each participant. The intensity for DTh, electrical pain threshold, and "Pain-4" (10 x DTh) were assessed and determined by applying single electrical pulses steps of 0.1 mA until the subjects reported electrical sensation, pain, and a pain rating of 4/10, respectively. Additionally, each subject was familiarized with the electrical pulses prior to assessment of electrical pain threshold.

For electrical TS, the subjects were instructed to assess the unpleasantness of the sensation as well as pain intensity using the NRS (0: no pain/discomfort; 10: maximum pain/discomfort) at 5 min intervals, before and up to 45 min after the HFS (see Figure 1). Thus, these assessments were performed at 5, 10, and 15 min before the HFS, and 5, 10, 15, 20, 25, 30, 35, 40, and 45 min after the HFS (Figure 1).

2.2.2.2 Mechanical and thermal TS

Mechanical TS were applied using a cotton bud (Q-tip, United States), brush (SenseLab 05, Somedic AB, Sweden), and a von Frey filament (Stoelting Co., United States; No. 5.88, nominal buckling force 588.2 mN) applied at the test sites to assess dynamic mechanical detection sensitivity (light touch sensation), dynamic mechanical allodynia (brushing), and mechanical pain sensitivity (pinprick), respectively. The sensation perceived with each mechanical stimuli at each test area was compared by the participant to the V2 dermatome (zygomatic bone) corresponding to the AIS Key Sensory Point (25) as an additional control area. The cotton bud was applied as one stroke (1–2 cm length) and the brush as 4 strokes (1–2 cm length) (1). The von Frey filament was placed perpendicularly to the tested surface for 1–2 s until it bent, and then kept in place for 2 additional seconds before the stimulus was removed (26). Aβ-fiber low-threshold mechanoreceptors and Aδ fiber nociceptors are predominantly activated by these mechanical TS (14).

Finally, thermal TS were applied using thermal rollers (Somedic SenseLab AB, Sösdala, Sweden; Roll-Temp II) at the test sites as strokes of 5 cm length to determine heat and cold sensitivity. The thermal rollers apply heat at 40°C and cold at 25°C. Aδ- and C-fiber afferents are predominantly activated by these thermal TS (14).

For thermal and mechanical TS, the subjects reported the perception at the test sites as compared to the V2 dermatome control area using a scale from 1 to 3 [i.e., (1) TS perceived as less intense than V2, (2) TS perceived as same intensity as V2, (3) TS perceived as more intense than V2]. This scale was adapted from validated scales used for standardized sensory examinations (27, 28). In addition, the pain intensity of the TS was assessed using the NRS (0: no pain; 10: maximum pain). Both sensory perception and pain intensity to TS were assessed at 5-min intervals before and up to 45 min after the HFS (Figure 1). Thus, these assessments were performed at 5, 10, and 15 min before the HFS, and 5, 10, 15, 20, 25, 30, 35, 40, and 45 min after the HFS (Figure 1).

2.3 Neuropathic sensations

The presence of neuropathic characteristics related to pain and induced by HFS was assessed with the seven items of the DN4 questionnaire: burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching (29). The participants rated the intensity of every neuropathic sensation using the NRS (0: absence; 10: maximum intensity) before and up to 45 min after the HFS. Thus, these assessments were performed at 5, 10, and 15 min before the HFS, and 5, 10, 15, 20, 25, 30, 35, 40, and 45 min after the HFS.

2.4 Levels of anxiety and depression

The Patient Health Questionnaire-9 (PHQ-9) and the 7-item generalized anxiety disorder (GAD) scale (GAD-7) were self-report instruments used to assess depression and anxiety, respectively, at baseline.

The PHQ-9 is a self-report screening test that includes nine items related to diagnostic criteria for major depression. The presence of depressed mood, anhedonia, sleep problems, feelings of tiredness, changes in appetite or weight, feelings of guilt or worthlessness, difficulty concentrating, feelings of sluggishness or worry, and suicidal ideation over the previous 2 weeks period were assessed with this questionnaire. Items are scored on a four-point Likert scale from 0 (never) to 3 (most days). Thus, total severity scores range from 0 to 27 points indicating moderate (10–14 points), moderately severe (15–19 points) and severe (20–27 points) levels of depressive symptoms (30, 31).

The GAD-7 includes 7 items related to anxiety symptoms rated on a 4-point response scale ranging from 0 ("never") to 3 ("nearly every day"). The total severity score ranges from 0 to 21 points indicating minimum (0–4), mild (5–9), moderate (10–14) and severe (15–21) anxiety (32, 33).

2.5 Perceived quality of life

Health-related quality of life was assessed with the paper-based five-level version of EuroQol-5D (EQ-5D-5L), which assesses independent daily activities, mobility, self-care, perceived pain, and depression/anxiety impact domains. All responses, ranging from 1 (absence of problems) to 3 (severe problems), were converted into a single index number, which corresponds to the health state according to standardized values ranging from 0 (health state equivalent to death) to 1 (optimal health) (34, 35). Additionally, this questionnaire also includes a visual analogue scale, where general health during the previous 24 h is rated on a scale from 0 (worse imaginable health) to 100 (best imaginable health) (35). This assessment was performed at baseline.

2.6 Statistical analysis

Data analysis was conducted using Sigma Plot version 11.0 (Systat Software, Inc., United States) and SPSS version 22.0 (IBM Corp., Armonk, New York, United States). Results are expressed as mean, standard deviation (SD), and standard error (SE). In general, the Shapiro–Wilk test revealed that quantitative data, except for TS

sensitivity, followed a normal distribution ($p > 0.05$). Measures of TS sensitivity were transformed into percentages; the scores of 1 to 3 were transformed to 33%, 66% and 100%, respectively. The repeated measures analysis of variance (RM-ANOVA) test followed by post-hoc pairwise tests using the Holm-Sidak correction was performed in order to investigate change in TS sensation, pain intensity following HFS, or pain intensity during HFS (trend of pain across time). General differences for TS sensations or pain intensity, and neuropathic sensations before and after HFS were calculated with the paired student's *t*-test. The interaction between dermatomal test site and time after HFS on TS sensation or pain intensity was analyzed with the two-way ANOVA. Additionally, the possible influence of baseline demographic or clinical characteristics on HFS-induced changes in sensation or pain intensity were analyzed with the χ^2 tests of independence, unpaired student *t*-test, and one-way ANOVA followed by post-hoc pairwise tests to control for multiple comparisons. Finally, the Pearson correlation (*r*) test was used to evaluate associations between variables. The statistical analysis was conducted at a 95% confidence level with a *p*-value <0.05 which was considered statistically significant.

3 Results

3.1 Demographic and clinical data of the participants

Twelve healthy subjects (50% women, mean age = 31 ± 15 years) were recruited. Clinical and demographic data are presented in Table 1. No significant differences in baseline characteristics were identified for age or sex, except for body mass index (BMI; $p = 0.034$): overweight individuals (BMI: 25.0–29.9) revealed higher PHQ-9 scores compared to normal weight (BMI 18.5–24.9) (7 ± 3.5 VS 3.86 ± 1.2).

3.2 Perception of CS

No visible skin injuries occurred following the electrical HFS, although skin blushing under the stimulated area was observed. Figure 2A shows pain ratings perceived during the HFS. The 100 Hz conditioning stimulation induced an increasing pain intensity during the HFS (temporal summation), i.e., when compared to the initial pain intensity rated with HFS value, a significant increase in pain intensity was perceived from 20 s up to 60 s.

3.3 Pain perception associated with electrical HFS: impact of age and quality of life

Figure 2A shows the mean (and SE) perceived pain intensity elicited during the HFS at ipsilateral C6 dermatome (dominant side; see Figure 1A). A significant increase in pain intensity was observed from 20 to 60 s (Figure 2A). The pain intensity perceived during the electrical HFS was significantly and positively associated with age ($r = 0.716$; $p = 0.009$): older individuals reported higher pain intensity during the electrical stimulus (Figure 2B). Individuals older than 40 years old perceived higher pain intensity during HFS compared to those subjects younger than 30 years old (8 ± 1 vs. 4.5 ± 1.9, $p = 0.02$). Additionally, a significant negative association was observed between pain intensity during HFS and perceived quality of life ($r = -0.633$; $p = 0.027$): subjects who reported poor quality of life perceived higher pain intensity with HFS (Figure 2C). No other significant differences in age range were found ($p > 0.05$) and no significant differences in BMI were revealed ($p > 0.05$).

3.4 Electrical HFS-induced changes in electrical pain sensitivity

Single electrical test applied stimuli at the ipsilateral C6 and contralateral C6 dermatomal test sites before and after electrical HFS revealed significant depotentiation of pain intensity (Figure 2D). A main effect of time was revealed: a significant decrease in perceived pain intensity was identified for the ipsilateral C6 dermatomes at 45 min and contralateral C6 test site at 45 min after HFS ($p < 0.01$). No significant potentiation was observed at 20 min after HFS for the ipsilateral test site. The percentage change in ipsilateral C6 pain intensity at 45 min after HFS is shown in Figure 2E.

Table 2 shows changes in electrical pain sensitivity reported by each participant at 5–15, 20–30 and 35–45 min after HFS: 75% of healthy individuals showed depotentiation between 35–45 min after HFS; however, 50% of participants demonstrated potentiation at 20–30 min interval after HFS.

3.5 Effect of electrical HFS on induced neuropathic sensations

During the 45 min after HFS, a significant increase in the number of neuropathic sensations were reported (0.6 ± 0.7 vs. 1.0 ± 0.8; $p = 0.023$), and especially when measured between 15 and 45 min after HFS (0.6 ± 0.7 vs. 1.0 ± 0.9; $p = 0.018$). The greatest change in frequency of neuropathic sensations was associated with tingling sensation: after HFS, the presence of tingling sensation tripled when compared in the pre-HFS interval (Figure 2F). No other significant changes were found.

3.6 Changes in mechanical and thermal sensitivity after HFS

Figure 3 reveals changes in mechanical sensitivity after HFS at the ipsilateral C6 dermatome test site (dominant side). No change in sensitivity was identified with brush (Figure 3A). In contrast, a significant increase in mechanical pain sensitivity (von Frey filament) at ipsilateral C6 dermatome (Figure 3B) was identified from 5 and up to 45 min after HFS. No other significant changes or significant differences among sites were found.

Figures 3, 4 reveal changes in thermal sensitivity after HFS at ipsilateral C6 and C7 dermatomes, and contralateral C6 dermatome. For cold sensitivity (Figure 3C), a significant main effect of time was revealed: a significant increase in cold sensitivity was found at the ipsilateral C6 dermatomes from 10 up to 40 min after HFS (Figure 3D). In addition, an increase in contralateral cold sensitivity at the C6 dermatome at 25 min after HFS was also identified. Additionally, some individuals also presented low pain intensity (NRS: 1–3) related to

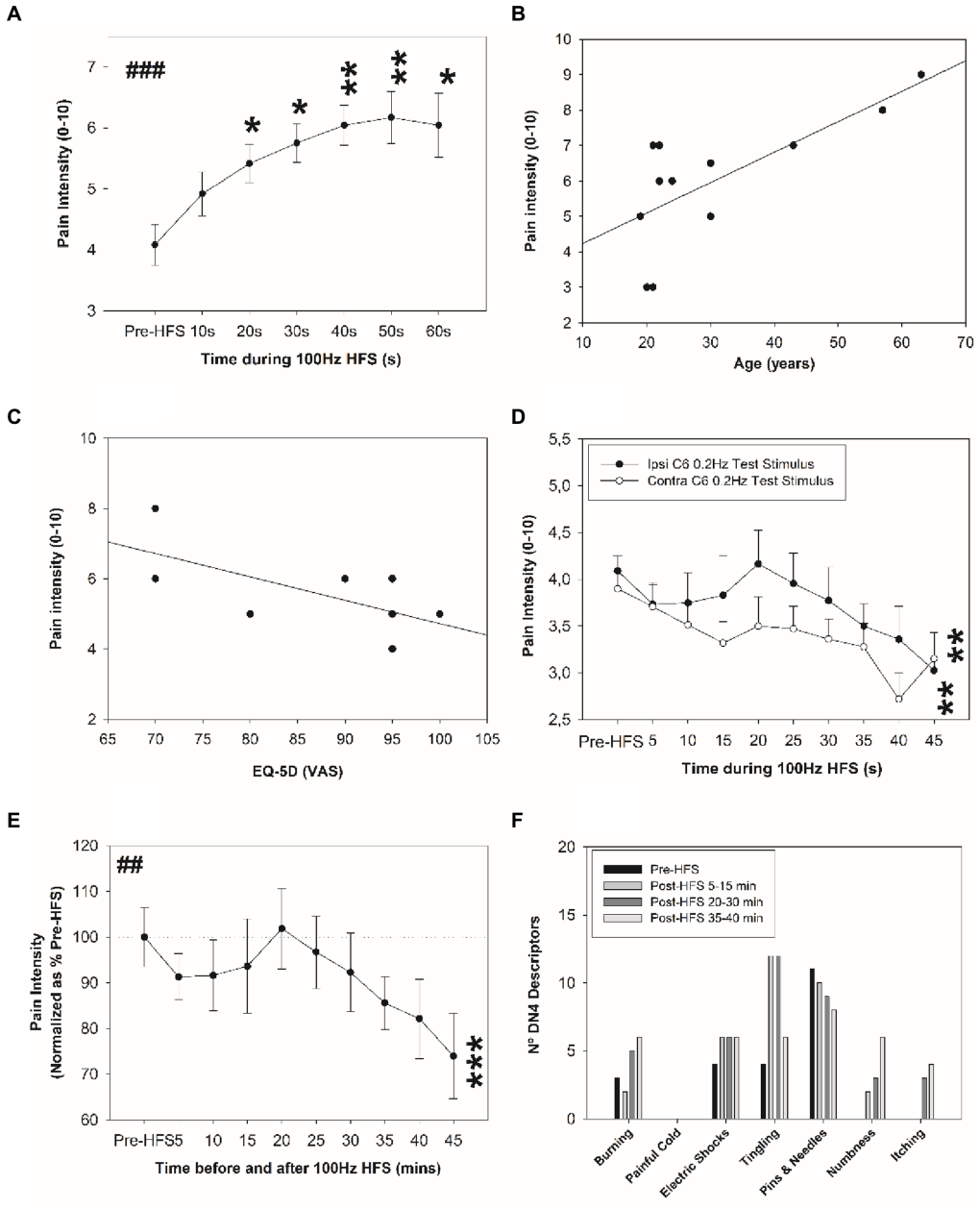

FIGURE 2
Change in electrical pain sensitivity after HFS. **(A)** Pain ratings perceived during HFS. Correlation between perceived pain intensity during the HFS and **(B)** age (years), and **(C)** health-related quality of life. **(D)** Perceived pain intensity elicited by the single electrical stimuli before and after HFS at the homotopic ipsilateral C6 dermatome site and at corresponding site in the contralateral arm. **(E)** Normalized perceived pain intensity elicited by the single electrical stimuli before and after HFS at the homotopic stimulation site. **(F)** Frequency of neuropathic sensations experienced before and after HFS. *$p < 0.05$, **$p < 0.01$, ##$p < 0.01$, ***$p < 0.001$ (RM-ANOVA ##, *post-hoc* pairwise tests *). Data presented as mean and standard errors.

cold hypersensitivity after HFS. No other significant changes were found in the ipsilateral C5 or C7 dermatomes.

3.7 Sex differences in sensitivity and pain intensity after HFS

Significant sex differences were found in cold sensitivity induced after HFS at C6 dermatome (dominant side), particularly between 15 and 45 min ($p = 0.02$): women showed higher cold sensitivity than men (3.0 ± 0.0 vs. 2.5 ± 0.8). Additionally, significant sex differences were found in mechanical pain sensitivity (pinprick) between 5 and 45 min after HFS at the C6 dermatome (dominant side, $p = 0.045$), particularly between 15–45 min ($p = 0.036$): women showed higher mechanical pain sensitivity than men (0.2 ± 0.04 vs. 0.0 ± 0.0). No other significant sex differences were found and no significant associations with levels of anxiety or depression were revealed.

TABLE 2 Change in individual electrical sensitivity during 100 Hz-HFS-induced potentiation or depotentiation presented as a percentage of the cohort pre-HFS pain intensity ($n = 12$).

Participant number	% pain modulation between 5–15 min	% pain modulation between 20–30 min	% pain modulation between 35–45 min
1	+48	+34	+34
2	+25	+26	-10
3	−49	−39	−51
4	−6	+7	+3
5	−3	−3	−3
6	−17	−46	−57
7	−31	−20	−40
8	−19	−14	−6
9	−21	−30	−58
10	+11	+70	+11
11	0	+23	−12
12	0	+3	−17
Potentiation (mean ± SE) and % of cohort presenting depotentiation	28.0 ± 10.8 (25)	32.0 ± 10.5 (50)	16.0 ± 9.3 (25)
Depotentiation (mean ± SE) and % of cohort presenting depotentiation	−20.9 ± 5.9 (58.3)	−25.3 ± 6.7 (50)	−29.6 ± 8.5 (75)

HFS, high-frequency stimulation; SE, standard error. The individual 100 Hz-HFS-induced potentiation or depotentiation was calculated as a percentage of the pre-HFS cohort normalized electrical pain intensity.

4 Discussion

Although the small sample size needs to be considered in the interpretation of the current findings, this study reveals for the first time simultaneous and significant long-lasting changes in cold sensitivity at the conditioned site and at the contralateral test site after electrical HFS. In addition, a possible sex and age effect on the perception of HFS pain and induced long-lasting changes in thermal and mechanical sensitivity were shown in healthy subjects. Importantly the use of electrical test stimuli sufficient to activate high-threshold afferent fibers has revealed a late development of pain depotentiation in electrical pain sensitivity at both the conditioned and contralateral test sites. Identification of a spectrum of long-term potentiation and depotentiation of multi-modal stimuli determines the need to better define both the conditioning and test stimuli parameters for the assessment of modulatory pain mechanisms.

4.1 HFS induces neuropathic sensations and long-lasting mechanical hyperalgesia

Electrical HFS increased the perception of neuropathic sensations, especially tingling as the most common neuropathic descriptor. Previously found hot and burning sensations were reported as the most common neuropathic descriptors (23), which were related to perceived pain intensity at the HFS site. These sensations have been attributed to the activation of Aδ-fibers and C-fibers (23).

This study also showed a significant increase in mechanical pain sensitivity at the HFS-conditioned site supporting similar findings observed around the HFS-conditioned site in previous studies (2, 3, 8), possibly mediated by Aδ fibers (3, 10, 13) and primary nociceptive C-fibers (3, 4, 12, 23, 36). Furthermore, long-lasting mechanical hypersensitivity to pinprick stimuli for more than 45 min has been reported previously (2), with an increase in pinprick-evoked brain potentials (37). Although the present findings should be considered with caution due to the small sample size, the results of the current study support the involvement of LTP in the mechanical sensitization at the conditioned site following electrical HFS.

After HFS, significant sex differences in mechanical and cold pain sensitivity were also revealed for the first time: women showed higher mechanical and cold pain sensitivity than in men. A previous study found no significant sex differences on HFS-induced pain sensitivity (13), although women showed a greater increase in mechanical pain sensitivity after electrical stimulation (13) and in pain sensitivity in general (38). Although the present findings need to be considered with caution due to the small sample size and further studies are needed to understand possible mechanisms underlying sex differences, pain perception during HFS could help to identify risk factors which underlie the development of chronic pain (39). This includes the possible association of pain perception during HFS with age and health-related quality of life.

4.2 HFS induces bilateral long-lasting sensitivity to cold stimuli

The current findings revealed a significant increase in cold sensitivity in both the ipsilateral and contralateral C6 dermatomes after HFS, unlike previous studies that reported no significant changes (14). The significant increase in cold sensitivity at the conditioned site could indicate a possible role for Aδ-fibers in cold sensitivity and hyperalgesia (40, 41) and thermal hyperalgesia at the stimulated area

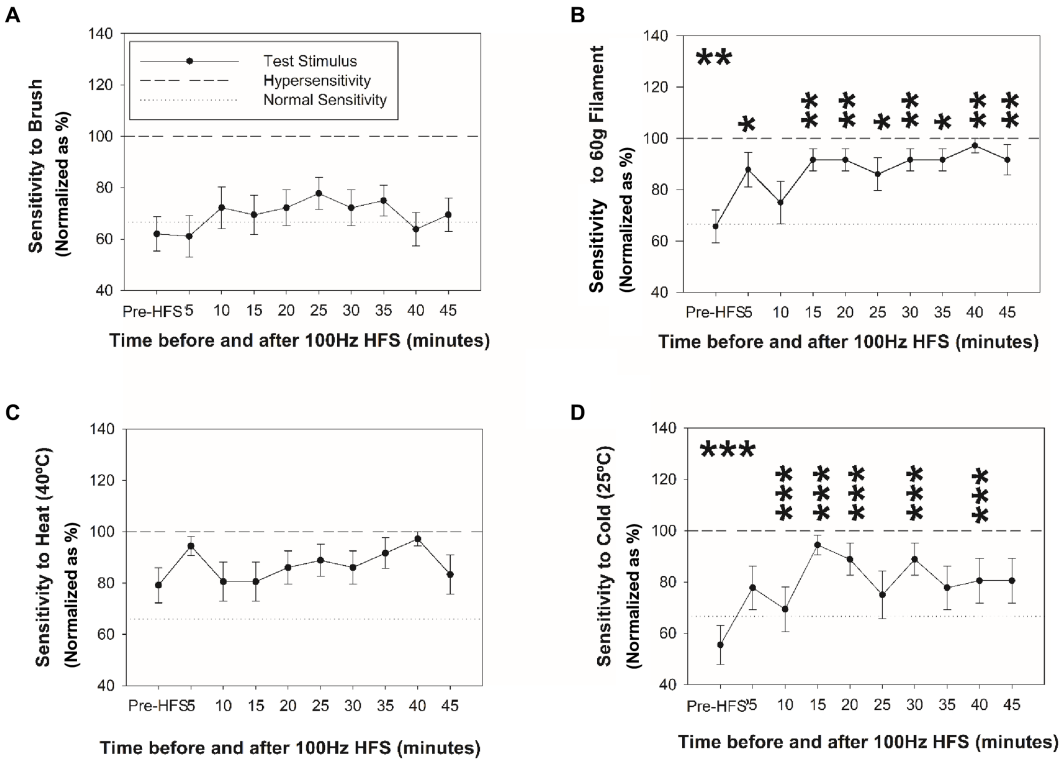

FIGURE 3
Changes in mechanical and thermal sensitivity after HFS. Sensitivity at the ipsilateral homotopic C6 dermatome before and after HFS to brush **(A)**, 60 g von Frey filament **(B)**, heat **(C)**, and cold stimuli **(D)**. *$p < 0.05$, **$p < 0.001$, ***$p < 0.001$ (RM-ANOVA, *post-hoc* pairwise tests). Data presented as mean and standard errors.

is a typical feature of primary hyperalgesia associated with this sensitization (4, 42). The observation of cold sensitivity in the contralateral dermatome could be explained that lumbar Lamina I neurons also receive contralateral afferent information (43), which may be disinhibited following periods of intense pain stimulation such as that applied with the electrical HFS stimulus (6, 7). This mechanism would lead to contralateral sensory information to projection neurons contributing to thermal hypersensitivity and mirror-image pain. Indeed, observations of cold hyperalgesia in participants with unilateral carpal tunnel syndrome have been observed (44) and quantitative sensory testing has revealed evidence for contralateral changes in sensitivity with different pain pathologies (6, 7). Similarly, HFS could also trigger LTP of unconditioned C-fiber synapses through glial cell processes (16). After HFS, no significant change in heat sensitivity was revealed supporting previous studies (2, 4, 14, 45). Nevertheless, the present findings should be considered with caution due to the small sample size.

4.3 HFS-induces long-term depotentiation of electrical pain intensity

The current study also found a significant depotentiation in electrical pain sensitivity at the conditioned and contralateral sites, supporting a concurrent reduction of the perceived pain intensity after HFS at the conditioned site and several remote test sites (5, 9–11), including the contralateral test area (5, 9, 10). Initial studies of HFS on electrical test stimuli revealed a long-term potentiation of pain intensity elicited by single electrical stimuli at the HFS site (1–3, 8, 13).

HFS could activate hypoesthesia induced by continuous electrical stimulation at C-fiber strength (4, 46). HFS could also reverse LTP with the induction of long-term depression (LTD) or LTP-induced depotentiation, depending on neuronal properties such as the membrane potential of spinal dorsal horn neurons (9), the type of cell activated demonstrated as LTP in spinothalamic neurons and LTD at GABAergic neurons (2, 47), and finally the implication of glia (48). Although the present findings should be considered with caution due to the small sample size, the recent observations of inhibition of electrical pain intensity at several test sites after HFS suggest that careful selection of test stimulus modality is critical to understanding processes of LTP and LTP-induced depotentiation in pain modulation.

4.4 Limitations

The small participant sample size requires some caution to be made in the interpretation and generalization of results from the present study. Nevertheless, sample size was based on sample sizes used in previous studies (3, 14), which even included smaller sample sizes (3). Furthermore, to our knowledge, this is the first study that has identified long-lasting changes in cold sensitivity after HFS at the conditioned site and contralateral test site. Further study of cold

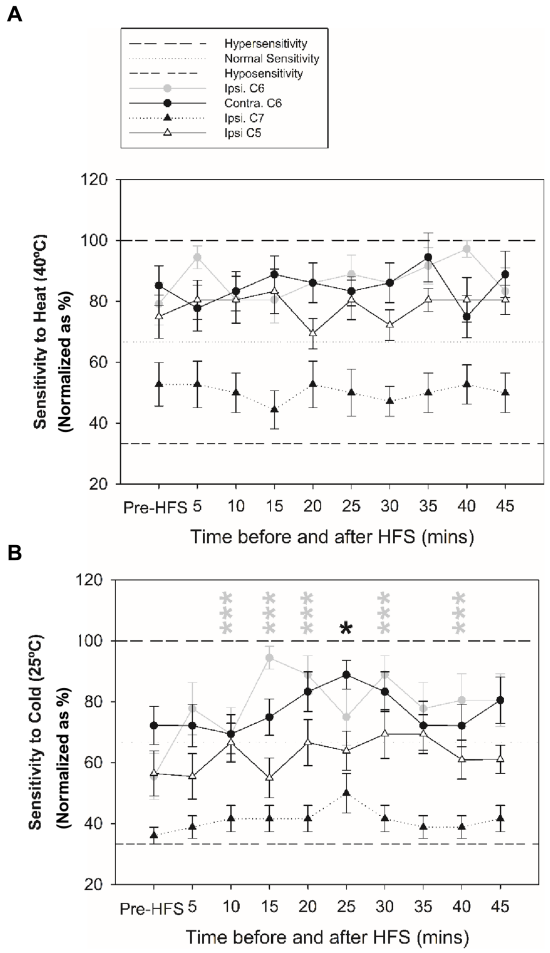

FIGURE 4
Changes in thermal sensitivity at ipsilateral C5, C6 and C7 dermatomes, and contralateral C6 test site before and after HFS. **(A)** Sensitivity to heat at ipsilateral before and after HFS. **(B)** Sensitivity to cold before and after HFS. *$p < 0.05$, ***$p < 0.001$ (RM-ANOVA, post-hoc pairwise tests). Data presented as mean and standard errors.

sensitization following HFS using quantitative sensory testing protocols may provide an important insight into the development of persistent pain mechanisms. In addition, the association of pain intensity experienced during HFS with age and quality of life, and the sex effect of induced pain sensitivity after HFS warrants further investigation into the influence of these demographic and clinical characteristics on LTP and pain sensitization in humans.

5 Conclusion

The present study revealed a significant long-lasting change in thermal, mechanical, and electrical sensitivity after HFS. These effects included a significant increase in mechanical pain sensitivity at the HFS-conditioned site, in addition to an increase in cold sensitivity and depotentiation in electrical pain sensitivity at both the ipsilateral and contralateral test dermatomes. In addition, changes in mechanical and cold sensitivity after HFS were dependent on sex. These results could lead to a better understanding of pathophysiological mechanisms in chronic pain pathologies in order to identify risk factors and to develop new management and prevention strategies for chronic pain. However, these results need to be considered with caution due to the small sample size. Future studies with larger sample sizes and chronic pain conditions are now required to confirm the current findings.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the local Clinical Research Ethics Committee (Approval number 149; 2022). This study was conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

IE-S: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. MR-L: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JT: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the MINECO (PID2020-119948RB-I00) and ADESLAS-Mutua Madrileña (2020).

Acknowledgments

The authors acknowledge technical help from Antonio Rodríguez-Moreno of the "Universidad Pablo de Olavide" and John Riddell of the University of Glasgow.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Pfau DB, Klein T, Putzer D, Pogatzki-Zahn EM, Treede RD, Magerl W. Analysis of hyperalgesia time courses in humans after painful electrical high-frequency stimulation identifies a possible transition from early to late LTP-like pain plasticity. *Pain*. (2011) 152:1532–9. doi: 10.1016/j.pain.2011.02.037

2. Xia W, Morch CD, Andersen OK. Exploration of the conditioning electrical stimulation frequencies for induction of long-term potentiation-like pain amplification in humans. *Exp Brain Res*. (2016) 234:2479–89. doi: 10.1007/s00221-016-4653-1

3. Klein T, Magerl W, Hopf HC, Sandkuhler J, Treede RD. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci*. (2004) 24:964–71. doi: 10.1523/JNEUROSCI.1222-03.2004

4. Xia W, Morch CD, Andersen OK. Test-retest reliability of 10 Hz conditioning electrical stimulation inducing long-term potentiation (LTP)-like pain amplification in humans. *PLoS One*. (2016) 11:e0161117. doi: 10.1371/journal.pone.0161117

5. van den Broeke EN, van Heck CH, Ceelen LA, van Rijn CM, van Goor H, Wilder-Smith OH. The effect of high-frequency conditioning stimulation of human skin on reported pain intensity and event-related potentials. *J Neurophysiol*. (2012) 108:2276–81. doi: 10.1152/jn.00391.2012

6. Enax-Krumova E, Attal N, Bouhassira D, Freynhagen R, Gierthmuhlen J, Hansson P, et al. Contralateral sensory and pain perception changes in patients with unilateral neuropathy. *Neurology*. (2021) 97:e389–402. doi: 10.1212/WNL.0000000000012229

7. Konopka KH, Harbers M, Houghton A, Kortekaas R, van Vliet A, Timmerman W, et al. Bilateral sensory abnormalities in patients with unilateral neuropathic pain; a quantitative sensory testing (QST) study. *PLoS One*. (2012) 7:e37524. doi: 10.1371/journal.pone.0037524

8. van den Broeke EN, van Rijn CM, Biurrun Manresa JA, Andersen OK, Arendt-Nielsen L, Wilder-Smith OH. Neurophysiological correlates of nociceptive heterosynaptic long-term potentiation in humans. *J Neurophysiol*. (2010) 103:2107–13. doi: 10.1152/jn.00979.2009

9. van den Broeke EN, Urdi M, Mouraux A, Biurrun Manresa JA, Torta DME. High-frequency electrical stimulation of cutaneous nociceptors differentially affects pain perception elicited by homotopic and heterotopic electrical stimuli. *J Neurophysiol*. (2021) 126:1038–44. doi: 10.1152/jn.00289.2021

10. van den Broeke EN, Vanmaele T, Mouraux A, Stouffs A, Biurrun-Manresa J, Torta DM. Perceptual correlates of homosynaptic long-term potentiation in human nociceptive pathways: a replication study. *R Soc Open Sci*. (2021) 8:200830. doi: 10.1098/rsos.200830

11. van den Broeke EN, van Heck CH, van Rijn CM, Wilder-Smith OH. Neural correlates of heterotopic facilitation induced after high frequency electrical stimulation of nociceptive pathways. *Mol Pain*. (2011) 7:28. doi: 10.1186/1744-8069-7-28

12. Henrich F, Magerl W, Klein T, Greffrath W, Treede RD. Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. *Brain*. (2015) 138:2505–20. doi: 10.1093/brain/awv108

13. Klein T, Stahn S, Magerl W, Treede RD. The role of heterosynaptic facilitation in long-term potentiation (LTP) of human pain sensation. *Pain*. (2008) 139:507–19. doi: 10.1016/j.pain.2008.06.001

14. Lang S, Klein T, Magerl W, Treede RD. Modality-specific sensory changes in humans after the induction of long-term potentiation (LTP) in cutaneous nociceptive pathways. *Pain*. (2007) 128:254–63. doi: 10.1016/j.pain.2006.09.026

15. van den Broeke EN, Mouraux A. High-frequency electrical stimulation of the human skin induces heterotopical mechanical hyperalgesia, heat hyperalgesia, and enhanced responses to nonnociceptive vibrotactile input. *J Neurophysiol*. (2014) 111:1564–73. doi: 10.1152/jn.00651.2013

16. Kronschlager MT, Drdla-Schutting R, Gassner M, Honsek SD, Teuchmann HL, Sandkuhler J. Gliogenic LTP spreads widely in nociceptive pathways. *Science*. (2016) 354:1144–8. doi: 10.1126/science.aah5715

17. Ruscheweyh R, Wilder-Smith O, Drdla R, Liu XG, Sandkuhler J. Long-term potentiation in spinal nociceptive pathways as a novel target for pain therapy. *Mol Pain*. (2011) 7:20. doi: 10.1186/1744-8069-7-20

18. Sandkuhler J. Translating synaptic plasticity into sensation. *Brain*. (2015) 138:2463–4. doi: 10.1093/brain/awv193

19. van den Broeke EN, Geene N, van Rijn CM, Wilder-Smith OH, Oosterman J. Negative expectations facilitate mechanical hyperalgesia after high-frequency electrical stimulation of human skin. *Eur J Pain*. (2014) 18:86–91. doi: 10.1002/j.1532-2149.2013.00342.x

20. Della Porta D, Vilz ML, Kuzminova A, Filbrich L, Mouraux A, Legrain V. No evidence for an effect of selective spatial attention on the development of secondary hyperalgesia: a replication study. *Front Hum Neurosci*. (2022) 16:997230. doi: 10.3389/fnhum.2022.997230

21. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

22. Jensen MPTJ, Romano JM, Fisher LD. Comparative reliability and validity of chronic pain intensity measures. *Pain*. (1999) 83:157–62. doi: 10.1016/S0304-3959(99)00101-3

23. Hansen N, Klein T, Magerl W, Treede RD. Psychophysical evidence for long-term potentiation of C-fiber and Adelta-fiber pathways in humans by analysis of pain descriptors. *J Neurophysiol*. (2007) 97:2559–63. doi: 10.1152/jn.01125.2006

24. Schilder A, Magerl W, Hoheisel U, Klein T, Treede RD. Electrical high-frequency stimulation of the human thoracolumbar fascia evokes long-term potentiation-like pain amplification. *Pain*. (2016) 157:2309–17. doi: 10.1097/j.pain.0000000000000649

25. Rupp R, Biering-Sorensen F, Burns SP, Graves DE, Guest J, Jones L, et al. International standards for neurological classification of spinal cord injury: revised 2019. *Top Spinal Cord Inj Rehabil*. (2021) 27:1–22. doi: 10.46292/sci2702-1

26. Van der Cruyssen F, Van Tieghem L, Croonenborghs TM, Baad-Hansen L, Svensson P, Renton T, et al. Orofacial quantitative sensory testing: current evidence and future perspectives. *Eur J Pain*. (2020) 24:1425–39. doi: 10.1002/ejp.1611

27. Reimer M, Forstenpointner J, Hartmann A, Otto JC, Vollert J, Gierthmühlen J, et al. Sensory bedside testing: a simple stratification approach for sensory phenotyping. *Pain Rep*. (2020) 5:e820. doi: 10.1097/PR9.0000000000000820

28. Kirshblum S, Didesch M, Botticello A, Kong B, Androwis D. Patient preferences for order of the sensory portion of the international standards for neurological classification of spinal cord injury (ISNCSCI) examination. *J Spinal Cord Med*. (2019) 42:719–24. doi: 10.1080/10790268.2019.1582602

29. Perez C, Galvez R, Huelbes S, Insausti J, Bouhassira D, Diaz S, et al. Validity and reliability of the Spanish version of the DN4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component. *Health Qual Life Outcomes*. (2007) 5:66. doi: 10.1186/1477-7525-5-66

30. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x

31. Muñoz-Navarro R, Cano-Vindel A, Medrano LA, Schmitz F, Ruiz-Rodriguez P, Abellan-Maeso C, et al. Utility of the PHQ-9 to identify major depressive disorder in adult patients in Spanish primary care centres. *BMC Psychiatry*. (2017) 17:291. doi: 10.1186/s12888-017-1450-8

32. Muñoz-Navarro R, Cano-Vindel A, Moriana JA, Medrano LA, Ruiz-Rodriguez P, Aguero-Gento L, et al. Screening for generalized anxiety disorder in Spanish primary care centers with the GAD-7. *Psychiatry Res*. (2017) 256:312–7. doi: 10.1016/j.psychres.2017.06.023

33. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. (2006) 166:1092–7. doi: 10.1001/archinte.166.10.1092

34. Rios-Leon M, Valera-Calero JA, Ortega-Santiago R, Varol U, Fernandez-de-Las-Penas C, Plaza-Manzano G. Analyzing the interaction between clinical, neurophysiological and psychological outcomes underlying chronic plantar heel pain: a network analysis study. *Int J Environ Res Public Health*. (2022) 19:10301. doi: 10.3390/ijerph191610301

35. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. (2012) 15:708–15. doi: 10.1016/j.jval.2012.02.008

36. van den Broeke EN, Mouraux A. Enhanced brain responses to C-fiber input in the area of secondary hyperalgesia induced by high-frequency electrical stimulation of the skin. *J Neurophysiol*. (2014) 112:2059–66. doi: 10.1152/jn.00342.2014

37. van den Broeke EN, Lambert J, Huang G, Mouraux A. Central sensitization of mechanical nociceptive pathways is associated with a long-lasting increase of pinprick-evoked brain potentials. *Front Hum Neurosci*. (2016) 10:531. doi: 10.3389/fnhum.2016.00531

38. Pieretti S, Di Giannuario A, Di Giovannandrea R, Marzoli F, Piccaro G, Minosi P, et al. Gender differences in pain and its relief. *Ann Ist Super Sanita*. (2016) 52:184–9. doi: 10.4415/ANN_16_02_09

39. Klein T, Magerl W, Treede RD. Perceptual correlate of nociceptive long-term potentiation (LTP) in humans shares the time course of early-LTP. *J Neurophysiol*. (2006) 96:3551–5. doi: 10.1152/jn.00755.2006

40. Ji G, Zhou S, Carlton SM. Intact Adelta-fibers up-regulate transient receptor potential A1 and contribute to cold hypersensitivity in neuropathic rats. *Neuroscience*. (2008) 154:1054–66. doi: 10.1016/j.neuroscience.2008.04.039

41. Mackenzie RA, Burke D, Skuse NF, Lethlean AK. Fibre function and perception during cutaneous nerve block. *J Neurol Neurosurg Psychiatry*. (1975) 38:865–73. doi: 10.1136/jnnp.38.9.865

42. Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog Neurobiol*. (1992) 38:397–421. doi: 10.1016/0301-0082(92)90027-C

43. Luz LL, Lima S, Fernandes EC, Kokai E, Gomori L, Szucs P, et al. Contralateral afferent input to lumbar lamina I neurons as a neural substrate for mirror-image pain. *J Neurosci*. (2023) 43:3245–58. doi: 10.1523/JNEUROSCI.1897-22.2023

44. de la Llave-Rincon AI, Fernandez-de-las-Penas C, Fernandez-Carnero J, Padua L, Arendt-Nielsen L, Pareja JA. Bilateral hand/wrist heat and cold hyperalgesia, but not hypoesthesia, in unilateral carpal tunnel syndrome. *Exp Brain Res*. (2009) 198:455–63. doi: 10.1007/s00221-009-1941-z

45. van den Broeke EN, Lenoir C, Mouraux A. Secondary hyperalgesia is mediated by heat-insensitive A-fibre nociceptors. *J Physiol*. (2016) 594:6767–76. doi: 10.1113/JP272599

46. De R, Maihofner C. Centrally mediated sensory decline induced by differential C-fiber stimulation. *Pain*. (2008) 138:556–64. doi: 10.1016/j.pain.2008.02.005

47. Kim HY, Jun J, Wang J, Bittar A, Chung K, Chung JM. Induction of long-term potentiation and long-term depression is cell-type specific in the spinal cord. *Pain*. (2015) 156:618–25. doi: 10.1097/01.j.pain.0000460354.09622.ec

48. Huang CC, Hsu KS. Progress in understanding the factors regulating reversibility of long-term potentiation. *Rev Neurosci*. (2001) 12:51–68. doi: 10.1515/revneuro.2001.12.1.51

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 09 May 2024
DOI 10.3389/fmed.2024.1385123

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RECEIVED 12 February 2024
ACCEPTED 16 April 2024
PUBLISHED 09 May 2024

CITATION
Li J, Li W and Zhuang L (2024) Natural biomimetic nano-system for drug delivery in the treatment of rheumatoid arthritis: a literature review of the last 5 years.
Front. Med. 11:1385123.
doi: 10.3389/fmed.2024.1385123

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Natural biomimetic nano-system for drug delivery in the treatment of rheumatoid arthritis: a literature review of the last 5 years

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized primarily by synovitis, leading to the destruction of articular cartilage and bone and ultimately resulting in joint deformity, loss of function, and a significant impact on patients' quality of life. Currently, a combination of anti-rheumatic drugs, hormonal drugs, and biologics is used to mitigate disease progression. However, conventional drug therapy has limited bioavailability, and long-term use often leads to drug resistance and toxic side effects. Therefore, exploring new therapeutic approaches for RA is of great clinical importance. Nanodrug delivery systems offer promising solutions to overcome the limitations of conventional drugs. Among them, liposomes, the first nanodrug delivery system to be approved for clinical application and still widely studied, demonstrate the ability to enhance therapeutic efficacy with fewer adverse effects through passive or active targeting mechanisms. In this review, we provide a review of the research progress on the targeting mechanisms of various natural biomimetic nano-delivery systems in RA therapy. Additionally, we predict the development trends and application prospects of these systems, offering new directions for precision treatment of RA.

KEYWORDS

rheumatoid arthritis, natural biomimetic, nano-system, drug delivery, treatment

1 Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by bilateral inflammation of multiple joints. It involves the infiltration of synovial inflammatory cells in local joint cavities, leading to tenosynovitis, cartilage destruction, and bone erosion (1). In addition to the progression of joint inflammation and cartilage destruction, the extra-articular system is frequently affected during the course of the disease (2). Conventional drugs including nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids (GCs), and biologics are currently used for RA treatment (3, 4). These medications predominantly aim to suppress the immune response or the inhibit specific inflammatory mediators in order to alleviate symptoms associated with RA. However, the efficacy of drug treatment limited by the drug's short effective half-life and its insufficient ability to specifically target diseased tissues, leading to poor clinical outcomes (5). Furthermore, upon *in vivo* administration, the drug is disseminated throughout the body, resulting in an elevated risk of side effects on extra-articular organs (6).

Nano-delivery systems emerge as a promising therapeutic strategy to enhance the efficacy of drugs and optimize their therapeutic outcomes. Clinical studies reported that nano-delivery

systems have made remarkable contributions to the treatment of diverse diseases (7–9). Nano-delivery systems enhance drug solubility, prolong drug circulation time, reduce drug clearance, and deliver drugs to disease sites in a controlled manner (10, 11). In recent years, the design of multifunctional nanocarriers with sophisticated targeted drug delivery capabilities or transformable properties has gained significant attention (12, 13). These advancements enable smart drug delivery and aim to enhance therapeutic efficacy for RA. In brief, the integration of an efficient drug with a nano-delivery system holds promising potential as a therapeutic approach. Importantly, in comparison to exogenous nano-delivery systems (14, 15), the utilization of natural biomimetic nano-system for drug delivery offers superior biocompatibility, reduced cytotoxicity, and non-immunogenicity (16, 17). In this review, we focus on the utilization of natural biomimetic nanomaterials in the field of drug delivery for RA treatment, and discuss their advantages and limitations.

2 Methods

An extensive literature review was undertaken to understand the natural biomimetic nano-systems for drug delivery in the treatment of RA. A literature search was conducted on ScienceDirect, PubMed, and Web of Science for literature published between 2019 and 2023, using the keywords natural biomimetic, drug, nucleic acid, RNA, delivery system, endogenous albumin, extracellular vesicle, cell membrane, genetically engineered membrane, viral vectors, non-viral vectors, and nanoparticles (NPs) combined with rheumatoid arthritis. Other available resources were also used to identify relevant articles.

3 Molecular mechanisms of RA pathogenesis

The occurrence and progression of RA are associated with dysregulated signaling pathways and autoimmune dysfunction. Abnormal regulation of signaling pathways (Figure 1), including MAPK, NF-κB, PI3K/AKT, JAK/STAT, among others, leads to abnormal expression of inflammatory cells and mediators such as fibroblast-like synoviocytes (FLSs), synovial macrophages, and other inflammatory mediators within the affected joint cavities (18). The interplay between multiple inflammatory cells and cytokines contributes to the inflammatory response in RA, leading to hyperactive immune system activity that drives the development and perpetuation of the disease (18, 19). In the early stages of RA pathogenesis, B cells secrete pro-inflammatory cytokines such as rheumatoid factor and anti-citrullinated protein antibody, which play a pivotal role in mediating T cell and macrophage activation (20). Upon activation, T cells and macrophages secrete inflammatory mediators such as tumor necrosis factor-α (TNF-α), matrix metalloproteinases (MMPs), interleukin-1 (IL-1) and IL-17. These mediators further exacerbate the inflammatory response, promote the formation of vascular opacities, and contribute to the damage of articular cartilage. In addition, immune cells such as dendritic cells and FLSs play a crucial role in mediating the pathophysiologic process of RA. In the advanced stages of immune system dysregulation during RA pathogenesis, these synovial cells undergo excessive proliferation and differentiate into tissue-invasive effector cells, thereby stimulating the formation of osteoclasts, ultimately resulting in progressive joint damage and the persistent presence of invasive inflammation within the synovial tissue (21).

4 Drugs delivery system

Based on the biological attributes of biomimetic units, natural biomimetic nano-systems offer three primary advantages: extended circulation within the body, precise targeting capabilities, and reduced toxicity. Currently, natural biomimetic nano-systems in the field of drug delivery for RA treatment including endogenous albumin, extracellular vesicles, cell membranes, and genetically engineered membranes. These innovative systems have demonstrated effectiveness in delivering therapeutic drugs or NPs to the affected joints, thereby enhancing the overall therapeutic outcome (Figure 2).

4.1 Endogenous albumin

Human serum albumin (HSA), the primary component of serum proteins, serves as a versatile carrier for therapeutic and diagnostic drugs with inflammation-targeting properties. Given its naturally biocompatibility, biodegradability, ease of production, and cost-effectiveness, HSA stands as a promising multifunctional drug carrier (22–24). In recent years, several preclinical studies have reported albumin-based biomimetic nano-systems as drug delivery vehicles for RA treatment in animal models (25–27).

A previous study revealed the overexpression of secreted protein, acidic and rich in cysteine (SPARC) in the synovial fluid and synovium of both RA patients and collagen-induced arthritis (CIA) mice (28). Moreover, augmented metabolism of synovial cells was observed in inflamed joints compared to healthy tissues, necessitating increased utilization of albumin for nitrogen and energy. These metabolic alterations in inflamed joints were found to be associated with the occurrence of hypoalbuminemia in RA patients. Consequently, the specific aggregation of albumin at inflammation sites can be attributed to increased blood albumin consumption, augmented permeability, and upregulated expression of SPARC.

In 2019, Liu and colleagues successfully developed HSA-NPs with specific targeting abilities to enhance the safety and therapeutic effectiveness of methotrexate (MTX) in CIA mice (29). Subsequently, Lyu et al. (30) and Chen et al. (31) developed two types of mannose-modified MTX-loaded HSA-NPs (MTX-M-NPs) to further augment the targeting capabilities of albumin NPs to inflammatory sites in animals. These targeted nano-systems enables the precise delivery of therapeutic agents to neutrophils specifically at the inflamed joint site by binding to the mannose receptor on the surface of neutrophils. Consequently, the utilization of MTX-M-NPs holds significant potential in enhancing the anti-inflammatory capabilities of neutrophils at the joint site in patients with RA. The application of albumin NPs in RA treatment was summarized in Table 1.

Albumin-based nano-systems offer advantages in enhancing targeted therapeutic efficacy at inflamed joint sites, as well as extending the half-life and improving the bioavailability of drugs. Fatty acids, such as palmitic acid, are commonly used to prolong the half-life of proteins or peptides. Accordingly, Gong et al. (36) synthesized

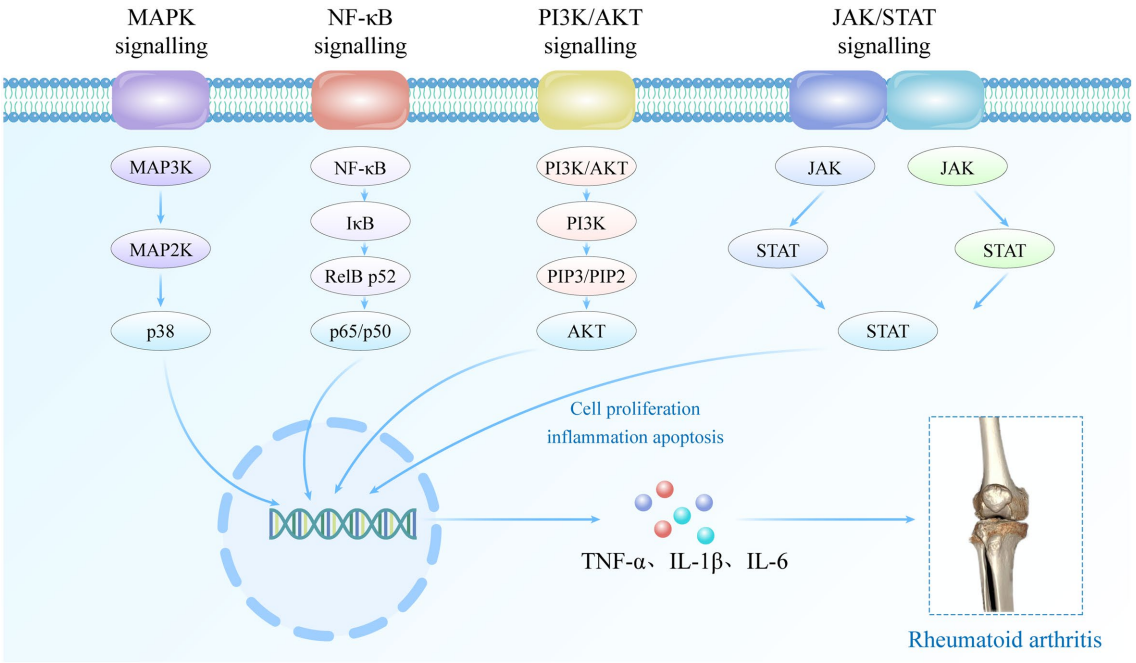

FIGURE 1
The role of signaling pathways in RA.

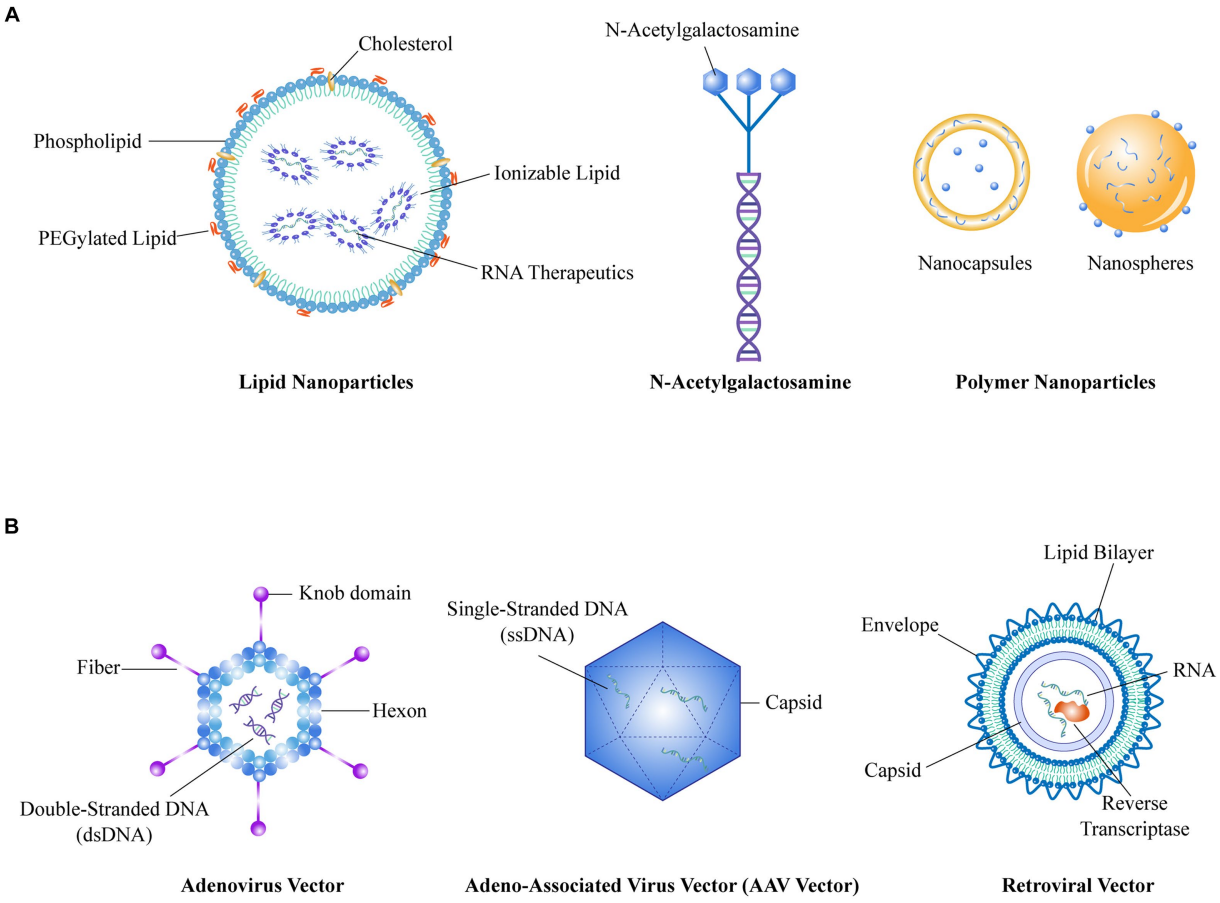

FIGURE 2
(A) Represents the schematic structure of a non-viral vector, **(B)** Represents the schematic structure of a viral vector.

TABLE 1 Application of albumin NPs in RA treatment.

NPs	Therapeutic advantages	Animal models
MTX-loaded albumin NPs (32)	MTX prodrug selectively binds to the cysteine-34 position of endogenous albumin and is efficiently cleaved by histone B and fibrinolytic enzymes overexpressed in RA and releases MTX.	CIA mice
Albumin-TRAIL coupling polymers (33)	Has significant targeted RA and long circulation	CIA mice
PAB-CLT (30)	PAB has significant SR-A targeting over BSA maleate (SR-A ligand)	AIA rat
HAS-PD/CU (34)	Accumulates in inflamed joints through the ELVIS effect and exhibits a slow release, synergistically delivering a high therapeutic effect at a low dose.	AIA rat
HAS-MTX (28)	Based on the high expression of SPARC in RA and the inherent high affinity of SPARC for albumin	CIA mice
MTX-M-NP_S (35)	Targeting of drugs to neutrophils by binding to mannose receptors	CIA rat

palmitic acid (PA)-modified bovine serum albumin (BSA) NPs (PAB-NPs). Through *in vivo* pharmacokinetic experiments, it was demonstrated that PAB-NPs significantly prolonged the drug's circulation time and improved its bioavailability compared to BSA-NPs. Targeting studies additionally revealed the prominent scavenger receptor-A (SRA) targeting properties of PAB-NPs, resulting in a remarkable 9.1-fold higher uptake of PAB-NPs by activated macrophages compared to BSA-NPs (36).

4.2 Extracellular vesicle

In recent years, significant advancements have been made in the field of RA treatment with regards to extracellular vesicles (EVs) (37, 38). These membrane-bound vesicles derived from various cells, play a crucial role as messengers in inter-cellular communication and the regulation of various pathophysiological conditions. EVs can be categorized into three primary subgroups based on their biological origin and size: exosomes (Exo, 30 to 200 nm), macrovesicles (MVs, 200 to 1,000 nm), and apoptotic vesicles (Avs, >1,000 nm) (39, 40). EVs can naturally be secreted by diverse cell types, such as macrophages and cancer cells, and are known for their non-cytotoxicity, non-immunogenicity, and excellent biocompatibility (41). In addition, the presence of consistent adhesion molecules on the EV surface facilitates preferential binding to host cells and helps them evade phagocytosis by endothelial reticulocytes (42, 43). EVs also play a crucial role in intercellular communication by transferring their cargo to various cells, thereby promoting cell transcription and proliferation (44). Therefore, the utilization of EVs as nano-systems for drug encapsulation can achieve effective drug delivery. Compared to cell-mediated nano-systems, EVs provide the advantage of reducing clearance by the mononuclear phagocyte system (MPS) and enhancing the accumulation of NPs in tissues (45).

Considering the involvement of macrophages in the inflammatory micro-environment of RA and their pro-inflammatory properties, researchers have explored the potential of using macrophage-derived EVs as drug carriers for RA treatment (46). Macrophages possess specific targeting properties due to the presence of surface membrane proteins, and EVs secreted by macrophages can inherit these targeting abilities from their host cells. Yan et al. (47) developed a biomimetic nanoparticle utilizing macrophage-derived Exo, wherein dexamethasone sodium phosphate (Dex) was encapsulated (Exo/Dex). The surface of these Exo was further modified with a folic acid (FA)-polyethylene glycol (PEG)-cholesterol (Chol) compound to create an active targeted drug delivery system known as FPC-Exo/Dex. Their results showed that the biomimetic drug delivery system exhibited an extended systemic circulation time for the drug, enhanced targeting efficiency at the site of inflammation, and offered enhanced protection against bone and cartilage damage in mice with CIA (47).

In another study, researchers utilized macrophage-derived micro vesicles (MMVs) encapsulated within NPs (MNPs) as a targeted approach for RA treatment (48). The proteomic profile of MMVs was analyzed using iTRAQ (isobaric tags for relative and absolute quantitation) labeling, providing insights into the relative and absolute protein levels. The presence of membrane proteins in MMVs that closely resemble those found on macrophage suggests that MMVs can exhibit similar biological activities to macrophage-targeted RA therapy. In addition, poly (lactic-co-glycolic acid; PLGA) NPs were encapsulated with MMVs, and the targeting efficacy of the MNPs system for inflammatory therapy was evaluated both *in vitro* and *in vivo*. Their results indicating that MNPs hold great promise as a biomimetic nano-delivery system for RA treatment (48). The application of EVs in RA treatment was summarized in Table 2.

4.3 Cell membrane

In recent years, there has been a surge of interest in the study of cell membrane-coated NPs owing to their remarkable biocompatibility, ability to retain cellular properties, and versatility in a wide range of therapeutic and imaging applications (50). Various immune cells have been identified to have crucial involvement in the progression of RA, and their cell membranes offer potential as nano-delivery systems with functionalities and targeting abilities. In addition, from a biological and immunological perspective, a novel interfacial attachment technique known as cell membrane capping technology has emerged as a promising approach to enhance the efficacy of synthetic nanocarriers (51). Apart from the extensively studied red blood cells (RBCs), various cell types such as platelets, white blood cells, cancer cells, stem cells, and even bacteria offer potential as sources for membrane materials, each possessing distinct properties and exerting diverse targeting characteristics (52, 53).

TABLE 2 Application of EVs NPs in RA treatment.

NPs	Therapeutic advantages	Animal models
IL-10-treated DC-derived exosomes (49)	Ability to inhibit the onset of arthritis and reduce the severity of established arthritis	CIA mice
FPC-Exo/Dex (44)	Targeted activation of FRβ expressed by macrophages inhibits the secretion of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines for better protection of bone and cartilage in CIA mice	CIA mice
MNP (45)	Enhancement of therapy by targeting ICAM-1 or p-selectin highly expressed by activated macrophages	CIA mice

TABLE 3 Application of cell membrane NPs in RA treatment.

NPs	Therapeutic advantages	Animal models
Neutrophil membrane-encapsulated PLGA NPs (57)	LFA-1 on neutrophil membranes binds to ICAM-1 and enhances targeting, a function-driven, broad-spectrum and disease-associated blocker that inhibits inflammatory cascades in disease processes	CIA mice/human TNF-α transgenic mice
Platelet membrane-encapsulated PLGA NPs (62)	Targeting disease sites by P-selectin and GVPI recognition	CIA mice
TU-NPs (63)	Neutralizes cytokines, inhibits synovial inflammation and provides strong cartilage protection to prevent joint-damaging substances from penetrating deep into inflamed tissues.	CIA mice

Upon coating with cell membranes, NPs not only acquire the physicochemical attributes of native cell membranes but also inherit distinctive biological functionalities arising from the presence of membrane-anchored proteins, antigens, and immune components (54, 55). The inherent biological properties and functions derived from these cell membrane-coated NPs, including immunosuppressive effects, prolonged circulation, and targeted recognition, underscore their significant potential in the field of biomedicine (56). Consequently, the development of a biomimetic nano-delivery system, emulating endogenous cells, holds promise for enabling molecular imaging and precise drug delivery to inflamed joint sites.

Erythrocytes, favored by researchers due to their remarkable circulatory longevity of up to 120 days, exhibit immense potential as carriers for drug delivery (57). Erythrocyte membrane-coated NPs have been proven to effectively extend the half-life in the systemic circulation, surpassing the performance of polyethylene glycol-coated nano-delivery systems (58). Li et al. reported a resveratrol-loaded PLGA NPs functionalized with erythrocyte membranes as a biomimetic delivery system significantly prolonged the circulation time of resveratrol in mice (32). During the last two decades, PEG has been the focus of studies due to its immunogenicity, which may trigger accelerated blood clearance (ABC) and hypersensitivity reactions to PEGylated NPs (59, 60). However, erythrocyte membrane-coated NPs are not affected by the "ABC" effect. The presence of CD47, a distinctive "do not eat me" protein expressed on the surface of RBCs, plays a crucial role in enabling the NPs to evade immune clearance by interacting with signal regulatory protein-α receptors (33). Furthermore, researchers have explored the intrinsic interaction between P-selectin expressed on platelets and inflamed tissues to develop platelet membrane NPs loaded with FK506 (tacrolimus), a potent immunosuppressant, for targeted treatment of RA at inflamed joint sites (34). These platelet membrane NPs exhibited prolonged drug circulation time in the bloodstream, enhanced accumulation at inflamed joint sites, and effectively mitigated joint swelling and inflammation.

In a previous study conducted by Dehaini, a novel bio-coating was developed using fused cell membranes of RBCs and platelets, resulting in RBC-platelet membrane NPs (49). The fused membrane combines the functionalities of erythrocytes and platelets, and experimental findings indicated that this carrier possesses properties from both cell sources. This innovative approach paves the way for the development of biomimetic nano-delivery systems with diverse functionalities, tailored to overcome existing limitations of nanoparticle-based therapeutic and imaging platforms (49).

Neutrophils have been observed to accumulate at inflammation sites in RA, and play an important role in reducing inflammation and repairing tissue damage (61). Zhang et al. developed neutrophil membrane-encapsulated NPs by fusing neutrophil membranes onto polymer cores (62). The resulting nano-delivery system retained the relevant membrane functions and antigenic properties of the host cells, making it an excellent candidate for targeted delivery to neutrophils. The NPs exhibited the ability to inhibit the secretion of pro-inflammatory cytokines, attenuate synovial inflammation, and provide protection against bone and cartilage damage in both CIA models and human transgenic arthritis mouse models (62). The application of cell membrane nano-system in RA treatment was summarized in Table 3.

4.4 Genetically engineered membrane

The advancements in naturally biomimetic nano-delivery systems have transformed cell membrane-coated NPs into a viable and practical therapeutic platform (64). In order to enhance the targeted delivery capabilities of nano-systems, it is possible to modify them with specific ligands that target inflammatory tissues or cells. However,

certain chemical or physical modifications may potentially disturb the structure or functionality of proteins present in cell membranes. Nevertheless, genetic engineering provides a means for the specific expression of targeted ligands onto cell membranes, without disrupting the existing membrane proteins. Taking advantage of this, researchers utilized genetic engineering techniques to generate cell membranes expressing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) from human umbilical vein endothelial cells (65). Subsequently, the fusion of the TRAIL-anchored membrane with hydroxychloroquine-loaded PLGA-NPs enables targeted delivery to activated M1 macrophages at the inflammation site, with the goal of therapeutically suppressing the secretion of pro-inflammatory. Following intravenous injection, the bionanoparticles were observed to accumulate and persist in the inflamed joints, leading to a favorable anti-inflammatory therapeutic outcome (65).

4.5 Bacteria

Remarkable progress has been made in the research of utilizing bacteria as a natural biomimetic nano-system for drug delivery in RA treatment. Studies primarily focus on harnessing the unique attributes of bacteria, such as their inherent targeting capabilities, programmability, and biocompatibility, to develop novel therapeutic approaches (66, 67). Through genetic engineering techniques, researchers have successfully engineered bacteria to target inflammatory sites in RA and subsequently release anti-inflammatory drugs or bioactive molecules, including anti-inflammatory proteins, immune modulators, siRNA, and miRNA, upon reaching the designated location. A preclinical study by Fan et al. developed an orally administered light-activated bacterial system that can specifically release TNF-α at inflammatory sites for tumor treatments, demonstrating the potential of utilizing bacteria for targeted therapy (68). Tao et al. presented a novel approach for the highly effective and dual-selective ablation of hypoxic tumors using engineered bacteria sensitized with near-infrared nanoantenna (69). These breakthrough methods hold promise as a new conceptual framework for potential applications in the treatment of RA.

In addition, outer membrane vesicles (OMVs) play crucial roles in various bacterial physiological activities and pathogenicity. Leveraging the physiological characteristics of OMVs, delivery of therapeutic substances such as siRNA, miRNA, and proteins to tissues has been achieved (70, 71). Effective liposomal nanocarriers designed through biotechnology methods have enhanced targeting drug delivery and immunogenicity through homologous and heterologous antigen modification (70). The lipid bilayer topology of liposomes allows for encapsulation of amphiphilic therapeutic drugs, which not only increases their stability and reduces side effects but also prolongs their half-life. Liposome encapsulation of adjuvant chemotherapy drugs for the treatment of colorectal cancer is considered a promising targeted drug delivery system. OMVs can serve as natural or engineered carriers of cell-protective factors or cytotoxins, making them a novel therapeutic tool applicable from regenerative medicine to targeted cancer therapy (72). To promote the release of therapeutic drugs under specific conditions, further research based on OMVs is required to engineer liposomal nano-carriers, thereby improving targeting specificity and increasing the uptake of therapeutic drugs.

While study on the use of bacteria-based nano-systems for drug delivery in the treatment of RA is currently limited, it is important to acknowledge the several key challenges that must be addressed before undertaking further studies. These challenges include ensuring the overall safety of bacterial carriers, improving delivery efficiency and precision, and achieving precise control over drug release. In summary, bacteria-based nano-systems hold great promise for the development of innovative treatments in the field of RA.

5 Nucleic acid delivery system

Nucleic acids are biocompatible materials with unique properties and structures. Small molecule nucleic acids such as sgRNA, siRNA, and shRNA can be specifically employed to silence target proteins, making them valuable tools for targeted delivery in nanomaterial applications. RNA is a versatile biomolecule present in biological cells as well as certain viruses and viroids. In a broader sense, RNA can be categorized into two types: coding RNA and non-coding RNA. Coding RNA refers to mRNA, which can be translated into proteins. On the other hand, non-coding RNA encompasses various types, including rRNA, tRNA, siRNA, miRNA, and antisense oligonucleotides (ASO), among others (73). In the field of drug research, small molecule drugs and protein-based therapeutics hold a dominant position, as these molecules function by acting on downstream target proteins of disease-causing genes. However, there is a lack of targeted drugs for many disease-related proteins, necessitating the exploration of more precise and effective therapeutic strategies.

The advent of RNA interference (RNAi) technology has revolutionized the ability to manipulate molecular processes with unprecedented precision (74). Compared to DNA, RNA is less stable and therefore requires more demanding delivery vehicles. Based on the composition of delivery system, RNA delivery vehicles can be broadly categorized into non-viral vectors and viral vectors (Figure 3; Table 4).

5.1 Non-viral vectors

Non-viral vectors primarily include lipid NPs (LNPs), N-acetylgalactosamine (GalNAc), polymer NPs (PNPs), and inorganic NPs (INPs) (75, 76). With their flexible size, shape, structure, low toxicity and accessible surface modification, non-viral vectors show great promise for application in RNA delivery. Among them, LNPs have found widespread application and are considered the optimal carriers for mRNA vaccines (75). However, their utilization is mainly limited to liver tissue targeting (77), and there is still a need for develop targeting capabilities toward extra-liver tissues. LNPs have been widely acknowledged as a promising delivery approach in the treatment of RA, as summarized in a previous review article (78).

5.2 Viral vectors

Viral vectors, consisting of adenovirus vectors (AdV), adeno-associated viral vectors (AAV), retroviral vectors (RV), and lentiviral

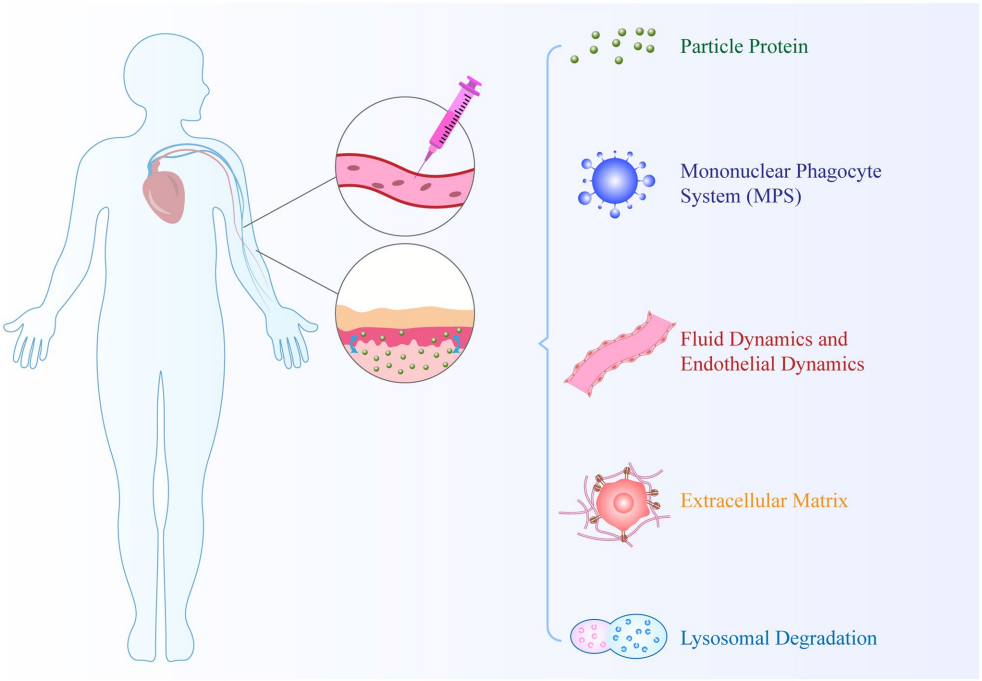

FIGURE 3
Biological transport barriers of nanodrug.

TABLE 4 Classification and characteristics of RNA Carriers.

Classification	NPs	Structure	Advantages	Disadvantages
Non-viral vectors	LNPs	Lipid vesicles with uniform lipid core	Uniform packaging, efficient intracellular and extracellular nucleic acid expression, high safety profile	Limited tissue targeting specificity
	GalNAc	Trivalent sugar compounds	Suitable for subcutaneous administration, scalable in manufacturing, with a high safety profile.	Limited to targeting hepatocytes
	PNPs	Product formed by polymerization of a monomer	Controlled drug release rate, biodegradable and biocompatible, with target specificity	Encapsulation High of toxicity, hydro residualphil organicic sol drugsvents, challenges insufficient in encaps largeulation of-scale hydro productionphilic, drugs and, issues challenges in with large storage-scale production and, and sterile issues withization storage
	INPs	Synthesis of Inorganic Particles and Biodegradable Polycation	Hydrophilic, biocompatible, and highly stable	Lack of clinical trial data, challenging clinical translation
Viral vectors	AdV	Large molecule double stranded uncoated icosahedral DNA virus	High thermal stability and strong ability to induce innate immunity, with only transient expression	immunogenicity, limited vector capacity, and restricted intracellular replication
	AAV	Icosahedral DNA deficient virus with non-enveloped single stranded linear structure	High safety profile, low immunogenicity, broad spectrum of infection, prolonged expression of exogenous genes *in vivo*	Limited size of the target gene fragment, delayed expression post host cell infection
	RV	Encapsulated spherical RNA virus	Broad infection spectrum, high specificity, high integration efficiency, capable of stable expression of the target gene	Presence of insertional mutations, potential risk of oncogene activation, with limited vector capacity
	LV	Encapsulated spherical RNA virus	Wider infection spectrum, high specificity, high integration efficiency, capable of stable expression of the target gene, with increased vector capacity	Presence of insertional mutations and potential risk of oncogene activation
Viral-like vector	VLP	Highly structured protein particles	High specificity and biological activity, high safety profile, high delivery efficiency	High immunogenicity

vectors (LV), are prominent vehicles for RNA delivery (79). These viral vectors possess advantages such as broad and targeted transduction capabilities, high delivery efficiency, and prolonged expression profiles. Among them, AAV vectors offer high delivery efficiency and have already been applied in clinical gene therapy for both *in vivo* and *ex vivo* applications, making them a relatively mature delivery technology (80). However, AAV vectors have limitations in terms of the size of the target gene fragment they can accommodate and the delayed onset of gene expression after infection of host cells, highlighting the need for ongoing optimization.

5.3 Viral-like vectors

Virus-like particle (VLP) vectors stand as an innovative gene therapy platform that has been developed in recent years, providing a novel approach for RNA delivery (81). VLPs are highly structured protein particles that self-assemble from one or multiple viral structural proteins. They resemble the morphology and structure of their corresponding natural viruses, thereby exhibiting strong immunogenicity, specificity, and biological activity (82, 83). Importantly, VLPs do not contain viral nucleic acids, rendering them incapable of replication and thus offering enhanced safety (84). The VLP delivery system utilizes the recognition principle between mRNA stem-loop structures and phage coat proteins. Through the utilization of viral engineering techniques, the advantages of both viruses and mRNA are synergistically combined, leading to the development of a novel delivery technology known as VLP-mRNA. This emerging platform has garnered significant attention as the next frontier in RNA delivery carriers.

6 Limitations and prospects

While nano-system for drug delivery holds immense potential in overcoming challenges in disease treatment and diagnostics by leveraging the properties of nanomaterials, some inherent limitations should be considered, particularly concerning the potential for cellular toxicity at the cellular level (85). Upon cell exposure, nanomaterials can cause varying degrees of cell damage, resulting in the generation of reactive species such as reactive nitrogen and oxygen species (86). Therefore, in addition to assessing the therapeutic properties of the drugs themselves, it is crucial to evaluate the toxicological impact of nanomaterials to ensure their safety. However, this process is costly and may block nanomedicines promoting to clinical trials.

Nanocarrier-based drug delivery systems encounter several biological barriers in drug transport. These transport processes occur within different compartments, such as within the cytoplasm and between compartments. As shown in Figure 4., biological barriers,

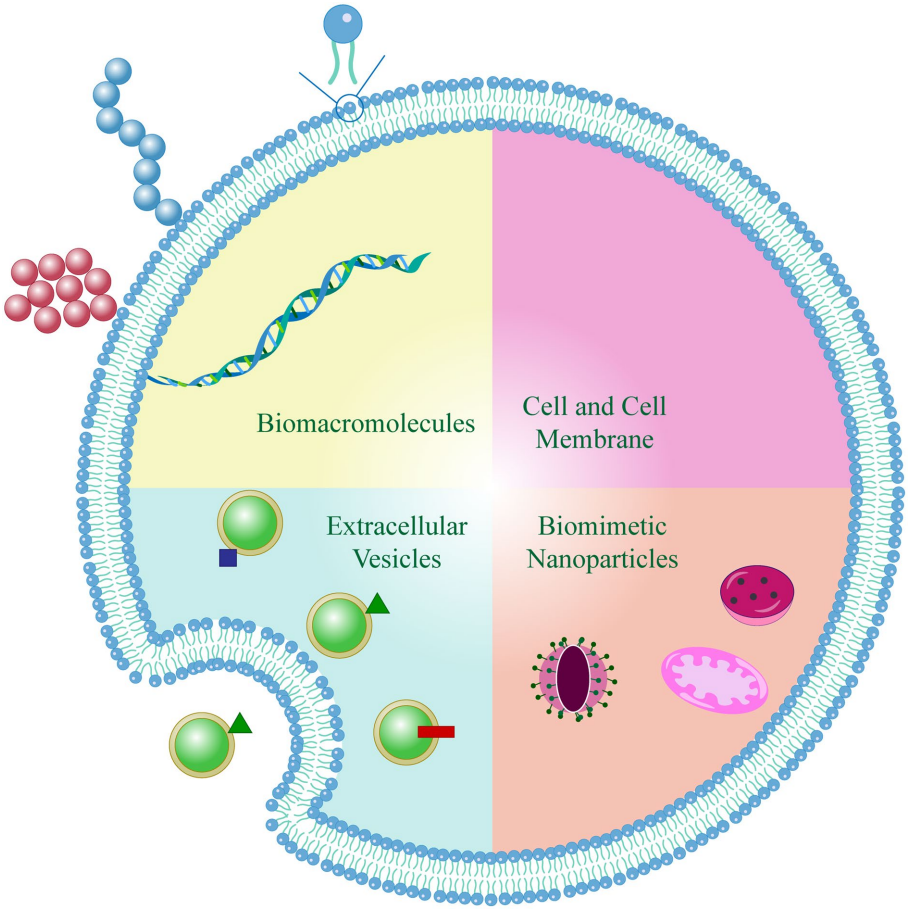

FIGURE 4
Basic unit of biomimetic nanoparticle design.

including cell membranes, nuclear membranes, and endosomal membranes, significantly interfere with drug delivery (87). Firstly, upon contact with biological fluids, NPs accumulate molecules on their surface and form a protein corona. The dynamic multi-layer protein structure of the protein corona provides NPs with specific identities, which can influence their physicochemical properties and subsequent biological interactions and distribution. Secondly, the activation of resident macrophages in the reticulate endothelial system (RES) aids in the clearance of old blood cells and substances carried in the blood circulation to RES organs. A key limitation of nanomedicines is their rapid phagocytosis and clearance based on the RES, resulting in a decrease in the bioavailability of nanodrugs. Thirdly, NPs face complex fluid dynamics when passing through curved and bifurcated regions of healthy or diseased blood vessels (88). Fourthly, the extracellular matrix provides tissues with structural integrity, characterized by high collagen content, rigidity, and tensile strength. It serves as a major natural physical barrier that hinders the delivery of nanodrugs. Finally, once NPs extravasate from blood vessels to the site of infection, they can bind to cell membranes, leading to internalization. This highlights the challenges faced by nanotechnology in drug delivery. However, the development of targeted nanomedicines that can directly deliver drugs to the inflamed site by targeting molecular constituents involved in RA pathophysiology or immune cells can potentially overcome these barriers.

7 Conclusion

The clinical treatment RA poses several challenges, making the development of endogenous substances as drug delivery systems necessary. Endogenous albumin, extracellular vesicles, cell membranes, nucleic acids, and bacteria have been chosen as biomimetic nano-delivery systems. These systems are preferred not only for their non-immunogenic and low toxicity properties but also for their capability to effectively evade immune system clearance and prolong drug circulation in the body. However, the use of bacteria as biomimetic nano-delivery systems is still in the exploratory stage, and several challenges need to be addressed, such as ensuring comprehensive safety of bacteria carriers, enhancing delivery efficiency and accuracy, and achieving precise control over drug release. Delivery carriers have improved the stability and target specificity of RNA formulations, thereby facilitating the clinical application of RNA-based therapeutics. Non-viral carriers, characterized by their low toxicity, high safety, large payload capacity, and design flexibility, offer several advantages. Among them, LNPs have wide-ranging applications and are considered the optimal carriers for mRNA vaccines. Viral carriers, on the other hand, exhibit broad-spectrum and strong targeting capabilities, high delivery efficiency, and sustained gene expression. Among viral carriers, AAV vectors have demonstrated high delivery efficiency and represent a relatively mature delivery technology. However, AAV vectors have limitations, such as restricted payload capacity for the target gene fragment and delayed expression after host cell infection, necessitating further optimization. VLP delivery strategies show great potential for efficient intracellular delivery of mRNA, offering broad applicability. In conclusion, further exploration is required to advance the clinical trials and applications of potential drug delivery systems in the field of RA, building upon existing biomimetic nano-delivery systems.

Author contributions

JL: Writing – review & editing. WL: Writing – review & editing. LZ: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Lin YJ, Anzaghe M, Schülke S. Update on the Pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. *Cells*. (2020) 9:880. doi: 10.3390/cells9040880

2. Kimbrough BA, Crowson CS, Davis JM 3rd, Matteson EL, Myasoedova E. *Decline in incidence of extra-articular manifestations of rheumatoid arthritis: A population-based cohort study*. Hoboken: Arthritis care res (2023).

3. Prasad P, Verma S, Surbhi Ganguly NK, Chaturvedi V, Mittal SA. Rheumatoid arthritis: advances in treatment strategies. *Mol Cell Biochem*. (2023) 478:69–88. doi: 10.1007/s11010-022-04492-3

4. Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. Eular recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis*. (2023) 82:3–18. doi: 10.1136/ard-2022-223356

5. Wang Z, Huang J, Xie D, He D, Lu A, Liang C. Toward overcoming treatment failure in rheumatoid arthritis. *Front Immunol*. (2021) 12:755844. doi: 10.3389/fimmu.2021.755844

6. Davis JM 3rd. The patient experience of drug side effects in rheumatoid arthritis: intriguing data from an exploratory online survey. *J Rheumatol*. (2022) 49:967–70. doi: 10.3899/jrheum.220412

7. Gowd V, Kanika J, Chaudhary AA, Rudayni HA, Rashid S, Khan R. Resveratrol and resveratrol nano-delivery systems in the treatment of inflammatory bowel disease. *J Nutr Biochem*. (2022) 109:109101. doi: 10.1016/j.jnutbio.2022.109101

8. Gu X, Gao Y, Wang P, Wang L, Peng H, He Y, et al. Nano-delivery systems focused on tumor microenvironment regulation and biomimetic strategies for treatment of breast cancer metastasis. *J Control Release*. (2021) 333:374–90. doi: 10.1016/j.jconrel.2021.03.039

9. Zare M, Norouzi Roshan Z, Assadpour E, Jafari SM. Improving the cancer prevention/treatment role of carotenoids through various nano-delivery systems. *Crit Rev Food Sci Nutr*. (2021) 61:522–34. doi: 10.1080/10408398.2020.1738999

10. Radu AF, Bungau SG. Nanomedical approaches in the realm of rheumatoid arthritis. *Ageing Res Rev*. (2023) 87:101927. doi: 10.1016/j.arr.2023.101927

11. Xiao S, Tang Y, Lv Z, Lin Y, Chen L. Nanomedicine - advantages for their use in rheumatoid arthritis theranostics. *J Control Release*. (2019) 316:302–16. doi: 10.1016/j.jconrel.2019.11.008

12. Liu Y, Chen L, Chen Z, Liu M, Li X, Kou Y, et al. Multifunctional Janus Nanoplatform for efficiently synergistic Theranostics of rheumatoid arthritis. *ACS Nano*. (2023) 17:8167–82. doi: 10.1021/acsnano.2c11777

13. Tao J, Yang P, Gao M, Zhang F, Wu Y, Jiang Y, et al. Reversing inflammatory microenvironment by a single intra-articular injection of multi-stimulus responsive lipogel to relieve rheumatoid arthritis and promote joint repair. *Mater Today Bio*. (2023) 20:100622. doi: 10.1016/j.mtbio.2023.100622

14. Kim J, Kim HY, Song SY, Go SH, Sohn HS, Baik S, et al. Synergistic oxygen generation and reactive oxygen species scavenging by manganese ferrite/ceria co-decorated nanoparticles for rheumatoid arthritis treatment. *ACS Nano*. (2019) 13:3206–17. doi: 10.1021/acsnano.8b08785

15. Wang P, Zhang Y, Lei H, Yu J, Zhou Q, Shi X, et al. Hyaluronic acid-based M1 macrophage targeting and environmental responsive drug releasing nanoparticle for enhanced treatment of rheumatoid arthritis. *Carbohydr Polym*. (2023) 316:121018. doi: 10.1016/j.carbpol.2023.121018

16. Tavasolian F, Moghaddam AS, Rohani F, Abdollahi E, Janzamin E, Momtazi-Borojeni AA, et al. Exosomes: effectual players in rheumatoid arthritis. *Autoimmun Rev*. (2020) 19:102511. doi: 10.1016/j.autrev.2020.102511

17. Wang K, Lei Y, Xia D, Xu P, Zhu T, Jiang Z, et al. Neutrophil membranes coated, antibiotic agent loaded nanoparticles targeting to the lung inflammation. *Colloids Surf B: Biointerfaces*. (2020) 188:110755. doi: 10.1016/j.colsurfb.2019.110755

18. Liu S, Ma H, Zhang H, Deng C, Xin P. Recent advances on signaling pathways and their inhibitors in rheumatoid arthritis. *Clin Immunol*. (2021) 230:108793. doi: 10.1016/j.clim.2021.108793

19. Sarapultsev A, Gusev E, Komelkova M, Utepova I, Luo S, Hu D. Jak-Stat signaling in inflammation and stress-related diseases: implications for therapeutic interventions. *Mol Biomed*. (2023) 4:40. doi: 10.1186/s43556-023-00151-1

20. Coutant F, Miossec P. Evolving concepts of the pathogenesis of rheumatoid arthritis with focus on the early and late stages. *Curr Opin Rheumatol*. (2020) 32:57–63. doi: 10.1097/BOR.0000000000000664

21. Jang S, Kwon EJ, Lee JJ. Rheumatoid arthritis: pathogenic roles of diverse immune cells. *Int J Mol Sci*. (2022) 23:905. doi: 10.3390/ijms23020905

22. Alghamri MS, Banerjee K, Mujeeb AA, Mauser A, Taher A, Thalla R, et al. Systemic delivery of an adjuvant Cxcr4-Cxcl12 signaling inhibitor encapsulated in synthetic protein nanoparticles for glioma immunotherapy. *ACS Nano*. (2022) 16:8729–50. doi: 10.1021/acsnano.1c07492

23. Gregory JV, Kadiyala P, Doherty R, Cadena M, Habeel S, Ruoslahti E, et al. Systemic brain tumor delivery of synthetic protein nanoparticles for glioblastoma therapy. *Nat Commun*. (2020) 11:5687. doi: 10.1038/s41467-020-19225-7

24. Song X, Qian H, Yu Y. Nanoparticles mediated the diagnosis and therapy of glioblastoma: bypass or cross the blood-brain barrier. *Small*. (2023) 19:e2302613. doi: 10.1002/smll.202302613

25. Gong T, Zhang P, Deng C, Xiao Y, Gong T, Zhang Z. An effective and safe treatment strategy for rheumatoid arthritis based on human serum albumin and Kolliphor(®) Hs 15. *Nanomedicine (London)*. (2019) 14:2169–87. doi: 10.2217/nnm-2019-0110

26. Kalashnikova I, Chung SJ, Nafiujjaman M, Hill ML, Siziba ME, Contag CH, et al. Ceria-based nanotheranostic agent for rheumatoid arthritis. *Theranostics*. (2020) 10:11863–80. doi: 10.7150/thno.49069

27. Zhao Y, He Z, Wang R, Cai P, Zhang X, Yuan Q, et al. Comparison of the therapeutic effects of gold nanoclusters and gold nanoparticles on rheumatoid arthritis. *J Biomed Nanotechnol*. (2019) 15:2281–90. doi: 10.1166/jbn.2019.2848

28. Rall LC, Rosen CJ, Dolnikowski G, Hartman WJ, Lundgren N, Abad LW, et al. Protein metabolism in rheumatoid arthritis and aging. Effects of muscle strength training and tumor necrosis factor alpha. *Arthritis Rheum*. (1996) 39:1115–24. doi: 10.1002/art.1780390707

29. Liu L, Hu F, Wang H, Wu X, Eltahan AS, Stanford S, et al. Secreted protein acidic and rich in cysteine mediated biomimetic delivery of methotrexate by albumin-based nanomedicines for rheumatoid arthritis therapy. *ACS Nano*. (2019) 13:5036–48. doi: 10.1021/acsnano.9b01710

30. Lyu J, Wang L, Bai X, Du X, Wei J, Wang J, et al. Treatment of rheumatoid arthritis by serum albumin nanoparticles coated with mannose to target neutrophils. *ACS Appl Mater Interfaces*. (2021) 13:266–76. doi: 10.1021/acsami.0c19468

31. Chen Z, Luo Z, Lyu J, Wang J, Liu Z, Wei J, et al. Preparation and formulation optimization of methotrexate-loaded human serum albumin nanoparticles modified by mannose. *Curr Med Chem*. (2021) 28:5016–29. doi: 10.2174/0929867328666210118112640

32. Li C, Wang X, Li R, Yang X, Zhong Z, Dai Y, et al. Resveratrol-loaded Plga nanoparticles functionalized with red blood cell membranes as a biomimetic delivery system for prolonged circulation time. *J Drug Delivery Sci Technol*. (2019) 54:101369. doi: 10.1016/j.jddst.2019.101369

33. Rao L, Bu LL, Xu JH, Cai B, Yu GT, Yu X, et al. Red blood cell membrane as a biomimetic Nanocoating for prolonged circulation time and reduced accelerated blood clearance. *Small*. (2015) 11:6225–36. doi: 10.1002/smll.201502388

34. He Y, Li R, Liang J, Zhu Y, Zhang S, Zheng Z, et al. Drug targeting through platelet membrane-coated nanoparticles for the treatment of rheumatoid arthritis. *Nano Res*. (2018) 11:6086–101. doi: 10.1007/s12274-018-2126-5

35. Ballantyne FC, Fleck A, Dick WC. Albumin metabolism in rheumatoid arthritis. *Ann Rheum Dis*. (1971) 30:265–70. doi: 10.1136/ard.30.3.265

36. Gong T, Tan T, Zhang P, Li H, Deng C, Huang Y, et al. Palmitic acid-modified bovine serum albumin nanoparticles target scavenger receptor-a on activated macrophages to treat rheumatoid arthritis. *Biomaterials*. (2020) 258:120296. doi: 10.1016/j.biomaterials.2020.120296

37. Dunshee LC, Sullivan MO, Kiick KL. Therapeutic nanocarriers comprising extracellular matrix-inspired peptides and polysaccharides. *Expert Opin Drug Deliv*. (2021) 18:1723–40. doi: 10.1080/17425247.2021.1988925

38. El-Jawhari JJ, El-Sherbiny Y, Mcgonagle D, Jones E. Multipotent mesenchymal stromal cells in rheumatoid arthritis and systemic lupus erythematosus; from a leading role in pathogenesis to potential therapeutic saviors? *Front Immunol*. (2021) 12:643170. doi: 10.3389/fimmu.2021.643170

39. Kanada M, Bachmann MH, Hardy JW, Frimannson DO, Bronsart L, Wang A, et al. Differential fates of biomolecules delivered to target cells via extracellular vesicles. *Proc Natl Acad Sci USA*. (2015) 112:E1433–42. doi: 10.1073/pnas.1418401112

40. Zhao L, Gu C, Gan Y, Shao L, Chen H, Zhu H. Exosome-mediated sirna delivery to suppress postoperative breast cancer metastasis. *J Control Release*. (2020) 318:1–15. doi: 10.1016/j.jconrel.2019.12.005

41. Belhadj Z, He B, Deng H, Song S, Zhang H, Wang X, et al. A combined "eat me/don't eat me" strategy based on extracellular vesicles for anticancer nanomedicine. *J Extracell Vesicles*. (2020) 9:1806444. doi: 10.1080/20013078.2020.1806444

42. Tang TT, Lv LL, Wang B, Cao JY, Feng Y, Li ZL, et al. Employing macrophage-derived microvesicle for kidney-targeted delivery of dexamethasone: an efficient therapeutic strategy against renal inflammation and fibrosis. *Theranostics*. (2019) 9:4740–55. doi: 10.7150/thno.33520

43. Tang TT, Lv LL, Wang B, Cao JY, Feng Y, Li ZL, et al. Erratum: employing macrophage-derived microvesicle for kidney-targeted delivery of dexamethasone: an efficient therapeutic strategy against renal inflammation and fibrosis: erratum. *Theranostics*. (2023) 13:870. doi: 10.7150/thno.78981

44. Kamerkar S, Lebleu VS, Sugimoto H, Yang S, Ruivo CF, Melo SA, et al. Exosomes facilitate therapeutic targeting of oncogenic Kras in pancreatic cancer. *Nature*. (2017) 546:498–503. doi: 10.1038/nature22341

45. Hegewald AB, Breitwieser K, Ottinger SM, Mobarrez F, Korotkova M, Rethi B, et al. Extracellular miR-574-5p induces osteoclast differentiation via Tlr 7/8 in rheumatoid arthritis. *Front Immunol*. (2020) 11:585282. doi: 10.3389/fimmu.2020.585282

46. Tardito S, Martinelli G, Soldano S, Paolino S, Pacini G, Patane M, et al. Macrophage M1/M2 polarization and rheumatoid arthritis: a systematic review. *Autoimmun Rev*. (2019) 18:102397. doi: 10.1016/j.autrev.2019.102397

47. Yan F, Zhong Z, Wang Y, Feng Y, Mei Z, Li H, et al. Exosome-based biomimetic nanoparticles targeted to inflamed joints for enhanced treatment of rheumatoid arthritis. *J Nanobiotechnol*. (2020) 18:115. doi: 10.1186/s12951-020-00675-6

48. Li R, He Y, Zhu Y, Jiang L, Zhang S, Qin J, et al. Route to rheumatoid arthritis by macrophage-derived microvesicle-coated nanoparticles. *Nano Lett*. (2019) 19:124–34. doi: 10.1021/acs.nanolett.8b03439

49. Dehaini D, Wei X, Fang RH, Masson S, Angsantikul P, Luk BT, et al. Erythrocyte-platelet hybrid membrane coating for enhanced nanoparticle functionalization. *Adv Mater*. (2017):29. doi: 10.1002/adma.201606209

50. Wang H, Liu Y, He R, Xu D, Zang J, Weeranoppanant N, et al. Cell membrane biomimetic nanoparticles for inflammation and cancer targeting in drug delivery. *Biomater Sci*. (2020) 8:552–68. doi: 10.1039/C9BM01392J

51. Li SY, Cheng H, Xie BR, Qiu WX, Zeng JY, Li CX, et al. Cancer cell membrane camouflaged Cascade bioreactor for Cancer targeted starvation and photodynamic therapy. *ACS Nano*. (2017) 11:7006–18. doi: 10.1021/acsnano.7b02533

52. Dhas N, García MC, Kudarha R, Pandey A, Nikam AN, Gopalan D, et al. Advancements in cell membrane camouflaged nanoparticles: a bioinspired platform for cancer therapy. *J Control Release*. (2022) 346:71–97. doi: 10.1016/j.jconrel.2022.04.019

53. Wang S, Wang Y, Jin K, Zhang B, Peng S, Nayak AK, et al. Recent advances in erythrocyte membrane-camouflaged nanoparticles for the delivery of anti-cancer therapeutics. *Expert Opin Drug Deliv*. (2022) 19:965–84. doi: 10.1080/17425247.2022.2108786

54. Jiang Q, Liu Y, Guo R, Yao X, Sung S, Pang Z, et al. Erythrocyte-cancer hybrid membrane-camouflaged melanin nanoparticles for enhancing photothermal therapy efficacy in tumors. *Biomaterials*. (2019) 192:292–308. doi: 10.1016/j.biomaterials.2018.11.021

55. Jiang Y, Krishnan N, Zhou J, Chekuri S, Wei X, Kroll AV, et al. Engineered cell-membrane-coated nanoparticles directly present tumor antigens to promote anticancer immunity. *Adv Mater*. (2020) 32:e2001808. doi: 10.1002/adma.202001808

56. Li SY, Cheng H, Qiu WX, Zhang L, Wan SS, Zeng JY, et al. Cancer cell membrane-coated biomimetic platform for tumor targeted photodynamic therapy and hypoxia-amplified bioreductive therapy. *Biomaterials*. (2017) 142:149–61. doi: 10.1016/j.biomaterials.2017.07.026

57. Jakobsson U, Mäkilä E, Rahikkala A, Imlimthan S, Lampuoti J, Ranjan S, et al. Preparation and in vivo evaluation of red blood cell membrane coated porous silicon nanoparticles implanted with (155)Tb. *Nucl Med Biol*. (2020) 84-85:102–10. doi: 10.1016/j.nucmedbio.2020.04.001

58. Wu X, Zhang X, Feng W, Feng H, Ding Z, Zhao Q, et al. A targeted erythrocyte membrane-encapsulated drug-delivery system with anti-osteosarcoma and anti-osteolytic effects. *ACS Appl Mater Interfaces*. (2021) 13:27920–33. doi: 10.1021/acsami.1c06059

59. Guo C, Yuan H, Wang Y, Feng Y, Zhang Y, Yin T, et al. The interplay between Pegylated nanoparticles and blood immune system. *Adv Drug Deliv Rev*. (2023) 200:115044. doi: 10.1016/j.addr.2023.115044

60. Miao G, He Y, Lai K, Zhao Y, He P, Tan G, et al. Accelerated blood clearance of Pegylated nanoparticles induced by peg-based pharmaceutical excipients. *J Control Release*. (2023) 363:12–26. doi: 10.1016/j.jconrel.2023.09.003

61. Xu TS, Jia SY, Li P. Interleukin-29 and interleukin-28A induce migration of neutrophils in rheumatoid arthritis. *Clin Rheumatol*. (2021) 40:369–75. doi: 10.1007/s10067-020-05211-3

62. Zhang Q, Dehaini D, Zhang Y, Zhou J, Chen X, Zhang L, et al. Neutrophil membrane-coated nanoparticles inhibit synovial inflammation and alleviate joint damage in inflammatory arthritis. *Nat Nanotechnol*. (2018) 13:1182–90. doi: 10.1038/s41565-018-0254-4

63. He M, Yu P, Hu Y, Zhang J, He M, Nie C, et al. Erythrocyte-membrane-enveloped biomineralized metal-organic framework nanoparticles enable intravenous glucose-responsive insulin delivery. *ACS Appl Mater Interfaces*. (2021) 13:19648–59. doi: 10.1021/acsami.1c01943

64. Brondello JM, Djouad F, Jorgensen C. Where to stand with stromal cells and chronic synovitis in rheumatoid arthritis? *Cells*. (2019) 8:1257. doi: 10.3390/cells8101257

65. Shi Y, Xie F, Rao P, Qian H, Chen R, Chen H, et al. Trail-expressing cell membrane nanovesicles as an anti-inflammatory platform for rheumatoid arthritis therapy. *J Control Release*. (2020) 320:304–13. doi: 10.1016/j.jconrel.2020.01.054

66. García-Álvarez R, Vallet-Regí M. Bacteria and cells as alternative nano-carriers for biomedical applications. *Expert Opin Drug Deliv*. (2022) 19:103–18. doi: 10.1080/17425247.2022.2029844

67. Lu H, Niu L, Yu L, Jin K, Zhang J, Liu J, et al. Cancer phototherapy with nano-bacteria biohybrids. *J Control Release*. (2023) 360:133–48. doi: 10.1016/j.jconrel.2023.06.009

68. Fan JX, Li ZH, Liu XH, Zheng DW, Chen Y, Zhang XZ. Bacteria-mediated tumor therapy utilizing Photothermally-controlled Tnf-α expression via Oral administration. *Nano Lett*. (2018) 18:2373–80. doi: 10.1021/acs.nanolett.7b05323

69. Tao C, Miao X, Yan J, Xiao X, Wu R, Cao Q, et al. Hypoxia-targeted and spatial-selective tumor suppression by near infrared nanoantenna sensitized engineered bacteria. *Acta Biomater*. (2023) 170:442–52. doi: 10.1016/j.actbio.2023.08.044

70. Micoli F, Maclennan CA. Outer membrane vesicle vaccines. *Semin Immunol*. (2020) 50:101433. doi: 10.1016/j.smim.2020.101433

71. Van Der Ley P, Schijns VE. Outer membrane vesicle-based intranasal vaccines. *Curr Opin Immunol*. (2023) 84:102376. doi: 10.1016/j.coi.2023.102376

72. Urabe F, Kosaka N, Ito K, Kimura T, Egawa S, Ochiya T. Extracellular vesicles as biomarkers and therapeutic targets for cancer. *Am J Phys Cell Phys*. (2020) 318:C29–c39. doi: 10.1152/ajpcell.00280.2019

73. Isenmann M, Stoddart MJ, Schmelzeisen R, Gross C, Della Bella E, Rothweiler RM. Basic principles of Rna interference: Nucleic acid types and in vitro intracellular delivery methods. *Micromachines (Basel)*. (2023) 14:14. doi: 10.3390/mi14071321

74. Wang M, Zhao J, Jiang H, Wang X. Tumor-targeted nano-delivery system of therapeutic Rna. *Mater Horiz*. (2022) 9:1111–40. doi: 10.1039/D1MH01969D

75. Eygeris Y, Gupta M, Kim J, Sahay G. Chemistry of lipid nanoparticles for Rna delivery. *Acc Chem Res*. (2022) 55:2–12. doi: 10.1021/acs.accounts.1c00544

76. Yan Y, Liu XY, Lu A, Wang XY, Jiang LX, Wang JC. Non-viral vectors for Rna delivery. *J Control Release*. (2022) 342:241–79. doi: 10.1016/j.jconrel.2022.01.008

77. Wang Y, Yin Z, Gao L, Ma B, Shi J, Chen H. Lipid nanoparticles-based therapy in liver metastasis management: from tumor cell-directed strategy to liver microenvironment-directed strategy. *Int J Nanomedicine*. (2023) 18:2939–54. doi: 10.2147/IJN.S402821

78. Chuang SY, Lin CH, Huang TH, Fang JY. Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. *Nanomaterials (Basel)*. (2018)8:42. doi: 10.3390/nano8010042

79. Wong B, Birtch R, Rezaei R, Jamieson T, Crupi MJF, Diallo JS, et al. Optimal delivery of Rna interference by viral vectors for cancer therapy. *Mol Ther*. (2023) 31:3127–45. doi: 10.1016/j.ymthe.2023.09.012

80. Kim SC, Kim A, Park JY, Hwang EM. Improved Aav vector system for cell-type-specific Rna interference. *J Neurosci Methods*. (2022) 368:109452. doi: 10.1016/j.jneumeth.2021.109452

81. Gutkin A, Rosenblum D, Peer D. Rna delivery with a human virus-like particle. *Nat Biotechnol*. (2021) 39:1514–5. doi: 10.1038/s41587-021-01124-x

82. Das S, Yau MK, Noble J, De Pascalis L, Finn MG. Transport of molecular cargo by interaction with virus-like particle Rna. *Angew Chem Int Ed Eng*. (2022) 61:e202111687. doi: 10.1002/anie.202111687

83. Zhitnyuk Y, Gee P, Lung MSY, Sasakawa N, Xu H, Saito H, et al. Efficient mrna delivery system utilizing chimeric Vsvg-L7Ae virus-like particles. *Biochem Biophys Res Commun*. (2018) 505:1097–102. doi: 10.1016/j.bbrc.2018.09.113

84. Hu Y, Lu B, Deng Z, Xing F, Hsu W. Virus-like particle-based delivery of Cas9/guide Rna ribonucleoprotein efficiently edits the brachyury gene and inhibits chordoma growth in vivo. *Discov Oncol*. (2023) 14:70. doi: 10.1007/s12672-023-00680-9

85. Higaki M, Ishihara T, Izumo N, Takatsu M, Mizushima Y. Treatment of experimental arthritis with poly(D, L-lactic/glycolic acid) nanoparticles encapsulating betamethasone sodium phosphate. *Ann Rheum Dis*. (2005) 64:1132–6. doi: 10.1136/ard.2004.030759

86. Wu Y, Wan S, Yang S, Hu H, Zhang C, Lai J, et al. Macrophage cell membrane-based nanoparticles: a new promising biomimetic platform for targeted delivery and treatment. *J Nanobiotechnol*. (2022) 20:542. doi: 10.1186/s12951-022-01746-6

87. Salimi M, Mosca S, Gardner B, Palombo F, Matousek P, Stone N. Nanoparticle-mediated Photothermal therapy limitation in clinical applications regarding pain management. *Nanomaterials (Basel)*. (2022) 12:922. doi: 10.3390/nano12060922

88. Gomez-Garcia MJ, Doiron AL, Steele RRM, Labouta HI, Vafadar B, Shepherd RD, et al. Nanoparticle localization in blood vessels: dependence on fluid shear stress, flow disturbances, and flow-induced changes in endothelial physiology. *Nanoscale*. (2018) 10:15249–61. doi: 10.1039/C8NR03440K

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 09 May 2024
DOI 10.3389/fmed.2024.1358829

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OPEN ACCESS

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RECEIVED 20 December 2023
ACCEPTED 08 April 2024
PUBLISHED 09 May 2024

CITATION
La Touche R, Paris-Alemany A, Pardo-Montero J, Miñambres-Martín D, Mercado-Romero F, de la Rosa-Díaz I, Sorrel MA and Grande-Alonso M (2024) The biobehavioural pain and movement questionnaire (BioPMovQ): development and psychometric validation of a new questionnaire.
Front. Med. 11:1358829.
doi: 10.3389/fmed.2024.1358829

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The biobehavioural pain and movement questionnaire (BioPMovQ): development and psychometric validation of a new questionnaire

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Objective: The purpose of this research was to design and psychometrically validate a new instrument (the Biobehavioural Pain and Movement Questionnaire/BioPMovQ), which assesses the relationship between pain and various factors related to motor behaviour from a biobehavioural perspective.

Methods: A mixed-method design combining a qualitative study with an observational and cross-sectional study was employed to develop (content validity) and psychometrically validate (construct validity, reliability and concurrent/discriminant validity) a new instrument. A total of 200 patients with chronic musculoskeletal pain were recruited.

Results: According to the exploratory factor analysis, the final version of the BioPMovQ consists of 16 items distributed across 4 subscales (1, disability, 2, self-efficacy for physical activity; 3, movement avoidance behaviours; and 4, self-perceived functional ability), all with an eigen value greater than 1, explaining 55.79% of the variance. The BioPMovQ showed high internal consistency (Cronbach's $\alpha = 0.82$; McDonald's $\omega = 0.83$). The intraclass correlation coefficient was 0.86 (95% confidence interval 0.76 to 0.91), which was considered to demonstrate excellent test–retest reliability. The standard error of measurement and minimal detectable change were 3.43 and 8.04 points, respectively. No floor or ceiling effects were identified. There was a positive, significant and moderate magnitude correlation with the Graded Chronic Pain Scale ($r = 0.54$), kinesiophobia ($r = 0.60$), pain catastrophising ($r = 0.44$) and chronic pain self-efficacy ($r = -0.31$).

Conclusion: The BioPMovQ showed good psychometric properties. Based on the findings of this study, the BioPMovQ can be used in research and clinical practice to assess patients with chronic musculoskeletal pain.

KEYWORDS

chronic pain, biobehavioural approach, self-administered questionnaires, psychological variables, functionality

1 Introduction

Pain is a complex multidimensional experience that significantly influences behaviour and has a perceptual character dependent on context and individual evaluative processes. In the multidimensional aspect of pain, movement is considered to play a key role (1). Simmonds et al. (2) considered that movement responses are not just a consequence of anticipating and minimising pain; the authors' proposed that the motor behaviour involved in pain is a very complex factor because psychological (cognition and emotions), social and contextual factors can influence motor activity within the behavioural component of pain as a multidimensional experience (2). Many psychological constructs are significant predictors of outcomes, such as pain, disability and work retention (3). These variables are relevant in a biobehavioural approach.

Several studies have reported the onset of functional and structural changes in the cortical motor areas of patients with chronic pain (4, 5). Pain-related movement disorders have been proposed to neurophysiologically involve central and peripheral mechanisms, which have varying degrees of influence in determining behavioural performance (6). There are also numerous studies on kinematic abnormalities associated with musculoskeletal pain (7–9).

In the past 2 decades, several theories have been developed to explain the relationship between pain and movement (10), which have been designed on the basis of findings from studies of experimentally induced pain (11) and on research assessing functional deficits and disability through the influence or interaction of sensory, cognitive, emotional and motor components in patients with chronic pain (12–16).

A number of authors have suggested the general premise that pain generates changes in the way patients move, which in turn can change the way patients perceive the painful experience (17–19), leading to the proposition that movement is initially involved in the experience of pain as an adaptive and protective response to control or diminish its perception (10, 20). These evoked responses can influence movement by altering neuromuscular speed, variability and efficiency. The theory of the motor behaviour dimension of the pain experience encompasses the set of adaptive or maladaptive motor responses related to the pain experience that affect modulation, processing and function and that also interact with or are influenced by contextual, cognitive and affective-motivational factors (1).

Emotional factors related to fear of pain play an important role in the degree of protective behaviours experienced when faced with pain (21). Research has shown that extreme fear of pain is associated with being less physically active (22, 23), having limited range of motion (24, 25), having greater physical disability (26) and developing strategies for adopting alternative movements (27). Behaviours associated with psychological distress, activity disruption and activity avoidance are essential components of pain-related disability (28).

Current evidence supports the fact that psychosocial factors other than fear of pain might contribute to pain-related functional impairment (29–31). Sullivan et al. suggested that certain psychological factors, such as pain catastrophising, fear and depression can influence pain behaviour by lowering the threshold for activating motor programmes related to the experience of pain (21).

Although more research is still needed to determine the complex interactions between movement and pain and their mutual influence on cognitive, behavioural and social factors, it is important to understand the relationship between movement and pain (32). It is now considered a clinical necessity to evaluate these interactions from a biobehavioural perspective, taking into account that pain-related movement disorders have a significant effect on the deterioration of the patient's functional capacity and quality of life (33).

Biobehavioural factors related to pain, functional limitation and disability can be classified into three broad categories: (1) cognitive-perceptual (cognitive-perceptual bias, perceived control, perceived disability, fear of pain, work and family perceptions and perceived self-efficacy); (2) behavioural-environmental (positive and negative behavioural consequences and physical stressors); and (3) physiological (physiological responses to work and physiological responses to pain or other aversive somatic stimuli) (33).

The central hypothesis of this research posits that the Biobehavioural Pain and Movement Questionnaire (BioPMovQ), specifically developed to evaluate the multifaceted impact of pain on movement from a biobehavioural standpoint, will demonstrate robust validity and psychometric properties, rendering it suitable for application in individuals suffering from musculoskeletal pain.

In light of the intricate interplay between pain, motor behaviour, and psychosocial factors in chronic musculoskeletal pain management, this study aims to address three primary objectives, each responding to a distinct need highlighted in the literature.

The first objective is to design a self-administered instrument assessing the impact of pain on various factors related to motor behaviour from a biobehavioural perspective. There are currently no valid and reliable assessment instruments that assess the multidimensional influence of pain on movement from a biobehavioural perspective. A single instrument that assesses various factors related to pain and movement (such as exercise self-efficacy, avoidance behaviours, physical discomfort, disability

and perceived functional ability) could be useful for clinicians involved in the study and treatment of pain.

The second objective, to evaluate the comprehension and content validity of the designed instrument, is rooted in the necessity to ensure that the instrument is both intelligible to patients and clinically relevant. This is pivotal to ensure that the measurements accurately reflect patients' experiences and are useful for health practitioners in clinical decision-making.

Lastly, the third objective aims to identify the basic psychometric properties of the instrument. This objective addresses the critical need for reliable and valid assessment tools to measure the complexities of musculoskeletal pain and its effects on motor behaviour. Psychometric validation is indispensable for advancing both research and clinical practice, enabling more tailored and effective interventions.

2 Methods

A mixed method design combining a qualitative study with an observational and cross-sectional study was employed to develop and psychometrically validate the new instrument. The design of the BioPMovQ was developed using a standardised methodology based on six phases (34): (1) perform an intensive literature review; (2) perform semi-structured interviews; (3) synthesise the literature review and analyse the semi-structured interviews; (4) develop the items (detail the items and identify the domains); (5) perform expert validation (content validity); and (6) assess the instrument's comprehension and feasibility (cognitive debriefing) in a small group of patients (pilot testing). The procedures during the psychometric validation were performed according to the COSMIN Study Design checklist for patient-reported outcome measurement instruments (35).

The study was approved by the bioethics committee of the Centro Superior de Estudios Universitarios La Salle (CSEULS-PI-005/2020). The objective of the research was explained to all participants in detail, who provided written informed consent to participate in the study. The data were collected between January 2020 and February 2022.

2.1 Development of the items

2.1.1 Literature review

A search of the scientific literature was performed in 6 specialised databases (Medline, PEDro, PsycINFO, CINAHL, EMBASE and Web of Science). Information was extracted from narrative reviews, qualitative studies, observational studies, systematic reviews and meta-analyses addressing the topics of pathophysiology of musculoskeletal pain, neurophysiology of chronic pain, pain-related motor impairments, function and disability, assessment of pain and movement and the social and psychological implications related to disability and functional ability.

The content analysis of the scientific literature was independently evaluated by 2 researchers who performed a tabular extraction of the relevant topics.

A second search was conducted to identify psychometrically validated self-report instruments aimed at identifying motor and functional implications related to pain, disability and psychosocial aspects. A total of 17 self-reporting instruments were identified and analysed in depth from a critical perspective, taking into account each instrument's differences, similarities, advantages, disadvantages and limitations (36–52).

2.1.2 Semi-structured interviews

Based on the scientific literature review, a semi-structured interview for patients with chronic musculoskeletal pain was designed by consensus. The interview was developed by focusing on the relationship between pain and movement function and possible psychosocial interference. Drafts of the interview questions were discussed and reviewed by the research team during a pre-established session. A semi-structured interview was conducted involving 12 patients with chronic musculoskeletal pain.

2.1.3 Synthesis of the literature review and semi-structured interview analysis

The results of the semi-structured interview were analysed, employing an interpretative phenomenological analysis (53), which is a qualitative study that assesses the meaning that people attach to their own experiences (54–56).

From the qualitative analysis, it was possible to extract the experiences and a construct meaning, and a list of three main themes and seven sub-themes was generated, which included (1) behaviours and cognitions of fear-avoidance; (2) pain-related changes in motor behaviours; (3) coping behaviours; (4) pain-related disability; (5) pain-related bodily perceptions; (6) self-efficacy related to activities of daily living; and (7) exercise self-efficacy.

The final analysis of this phase was performed by 2 researchers who, through a consensus methodology, grouped and sorted the results of the qualitative study and literature review.

From the synthesis of scientific evidence obtained through literature review, five fundamental conclusions can be drawn:

1 A multitude of studies have delineated or hypothesised various neurophysiological mechanisms, both central and peripheral, associated with pain. These mechanisms might be linked to alterations in movement and functionality, such as changes in motor control, range of movement, muscle strength and endurance, as well as the onset of disability.
2 Various factors influencing motor behaviour associated with pain—such as disability, avoidance behaviours, movement fear, and deficits in self-efficacy—can significantly impact patient quality of life. These factors are interconnected with multiple psychological aspects.
3 Disability is identified as a crucial factor in the analysis of patients with chronic pain, highlighting how these individuals face challenges in performing daily activities, recreational activities, physical activities, and work-related tasks.
4 Motor and functional alterations associated with pain could be conceptualised as a multidimensional construct that encompasses cognitive, emotional, sensory, and social dimensions.
5 Currently, there are no psychometrically validated instruments available that comprehensively assess the implications of motor and functional alterations associated with pain from a multidimensional perspective. There are various instruments that specifically and separately evaluate disability, self-efficacy in different pain-related contexts (physical activity, exercise,

pain self-management) and factors associated with fear and activity avoidance.

2.1.4 Developing items

Findings from the relevant literature and data from the semi-structured interviews were qualitatively analysed by 3 researchers to define the conceptual construct of "pain related to movement and function from a biobehavioural perspective." Subsequently, the articles were written. A total of 28 items were designed through a structured consensus process (57), with 27 items ultimately established for this phase and ordered by their relevance within each dimension (sub-constructs).

2.1.5 Expert-validated content

A 26-item preliminary list was drafted for the scale, the suitability of which (relevance, pertinence, clarity, coherence and degree of coverage of the relevant aspects) was evaluated by an external expert panel (validation by judges). The requirements to be considered an expert judge were (1) having at least 4 publications related to chronic pain, movement and function; (2) at least 10 years of clinical or scientific experience in the area of pain and movement; and (3) knowledge about the psychometric validation of questionnaires.

The expert content validation panel consisted of 11 expert judges with research and clinical backgrounds (1 medical doctor, 7 physiotherapists and 3 psychologists), who were asked to conduct a qualitative evaluation (relevance, comprehensiveness and comprehensibility) of every item, using a 5-level Likert scale (1, strongly agree; 2, agree; 3, neither agree nor disagree; 4, disagree; and 5, strongly disagree).

To consider an item for deletion, the following performance indicators were considered: (1) mean item score of <0.70 Aiken's V statistic (58); (2) the behavioural content did not have a generally accepted meaning or definition; (3) the item was ambiguously defined; (4) the content item was irrelevant or repetitive to the purposes of measurement; and (5) whether the qualified judges had agreed that the item had been adequately sampled based on consensus.

2.1.6 Cognitive debriefing

A cognitive debriefing methodology was applied as a qualitative evaluation of the preliminary version of the instrument by a small group of patients (32 patients). The cognitive debriefing was based on the instrument's evaluation, considering 5 aspects that analyse the completeness, relevance and clarity of expression (59): (1) comprehension of each question; (2) relevance of the information; (3) decision processes (response time, response/abandonment rate); (4) response processes; and (5) general comments.

2.2 Psychometric validation

2.2.1 Participants

A consecutive non-probability sample of participants were recruited from 2 physiotherapy clinics. All participants were assessed by physiotherapists with experience and academic training in managing musculoskeletal disorders, and the patients were classified as having chronic musculoskeletal pain. Chronic musculoskeletal pain is defined as "persistent or recurrent pain arising as part of a pathological process that directly affects the bones, joints, muscles or related soft tissues" (60).

Patients were selected if they met all the following criteria: (1) presence of pain of more than 6 months' duration; (2) a pain intensity greater than or equal to 3 points on the numerical pain rating scale (NPRS); (3) an age of 18 years or older; (4) chronic primary musculoskeletal pain, classified as primary chronic pain (cannot be directly attributed to a known disease or damage process) or as secondary if caused by a disease or process that directly affects the bones, joints, muscles and/or related soft tissues (61); (5) a good understanding of the Spanish language; and (6) not having started physiotherapy or having undergone fewer than 2 treatment sessions.

The exclusion criteria were (1) cognitive impairment; (2) psychiatric limitations that impede participation in the study assessments; (3) inability to grant written informed consent; (4) a history of musculoskeletal trauma (e.g., fracture); (5) postoperative musculoskeletal pain during the previous 6 months; and (6) musculoskeletal pain suspected to originate from neurological (e.g., stroke), neoplastic (e.g., breast cancer) and/or referred pain (e.g., visceral referred pain).

2.2.2 Sample size

The sample size for the psychometric evaluation was specifically established through a theoretical profile based on exploratory factorial analysis. We estimated that the sample size should exceed 200 cases based on a moderate condition where communalities of between 0.40 and 0.70 and at least 2 factors with more than 4 items each are expected (62). This estimate is in line with the methodological criteria of experts who consider that even under ideal conditions, such as obtaining high communalities and well-determined factors, the sample for studies that perform a factorial analysis should exceed 200 cases (62, 63).

For the sample size calculation for the test–retest reliability study, we employed the method described by Walter et al. (64), which is based on estimating the sample size from assumptions of the intraclass correlation coefficient (ICC) result. The minimum acceptable ICC estimated for the test–retest assessments (2 assessments) was $P0 = 0.75$; however, we expected an ICC higher than $P1 = 0.90$. Considering a power of 95% ($\beta = 0.5$) and an alpha error level of 0.05, the study sample size should comprise 45 participants; after estimating possible losses of 15% for the sample, the total recommended sample size is 53 participants. The sample size was calculated with a web calculator (65).

2.2.3 Procedure

After consenting to participate in the study, the recruited participants received a series of self-reports to assess disability-related and other psychological variables, as well as to record demographic characteristics. The self-reports included the preliminary version of the BioPMovQ, the Spanish version of the Chronic Pain Self-Efficacy Scale (CPSS), the Spanish version of the Pain Catastrophising Scale (PCS), the Spanish version of the Tampa Scale for Kinesiophobia (TSK-11) and the Spanish version of the Graded Chronic Pain Scale (GCPS).

The sociodemographic questionnaire collected information on gender, date of birth, marital status, educational level and employment status.

Biobehavioural Pain and Movement Questionnaire (BioPMovQ) (Draft version).

The preliminary version of the BioPMovQ consisted of 25 items and 5 theoretical subscales (factors) that evaluated (1) movement avoidance behaviours; (2) self-efficacy for physical activity; (3) physical discomfort; (4) self-perceived functional ability; and (5) disability. The items were scored on a 5-level Likert scale (1, strongly agree; 2, agree; 3, neither agree nor disagree; 4, disagree; and 5, strongly disagree). Higher scores indicate greater implications for pain-related motor and functional impairment.

2.3 Data analysis

The theoretical construct was determined and its reliability and external validity evaluated using SPSS software version 21 (IBM SPSS Statistics). Descriptive statistics were employed to summarise the data for categorical variables as absolute (number) and relative frequencies (percentage). Sociodemographic and clinical variables are presented as mean ± standard deviation (SD), 95% confidence interval, range (minimum-maximum), Skewness and Kurtosis. A normality analysis was conducted using the Kolmogorov–Smirnov test.

2.3.1 Construct validity

The construct validity was evaluated using an exploratory factor analysis (EFA) to determine the optimal factor structure. The factorial structure was investigated using Generalised Least Squares factoring (66) with OBLIMIN rotation. (67) The quality of the factor analysis models was assessed with the Kaiser–Meyer–Olkin (KMO) test and the Bartlett sphericity test. The KMO measures the degree of multicollinearity and ranges from 0 to 1 (with an optimal range of >0.50–0.60) (68). We established the optimal number of factors based on Kaiser's eigenvalue criterion (eigenvalue ≥1), evaluation of the scree plot (69), parallel analysis (70), and exploratory graph analysis (EGA); (71) and by choosing stable factors (more than 2 items per factor, lowest number of cross-loadings). These, parallel analysis and EGA, were executed using the psych and EGAnet R packages (72, 73). To evaluate the fit of the model to the data, a semi-confirmatory parallel analysis was conducted utilising various fit indices. The Root Mean Square Error of Approximation (RMSEA) was calculated, with a 90% Confidence Interval (CI). Typically, RMSEA values up to 0.08 are considered to indicate a reasonable fit to the data, with values closer to 0.05 or below suggesting a good fit. The Tucker-Lewis Index (TLI) was also determined. This index compares the fit of the proposed model to a null or baseline model. TLI values approaching or exceeding 0.95 are commonly viewed as indicative of an excellent fit to the data. The Bayesian Information Criterion (BIC) was computed as an additional measure of fit. Lower BIC values (more negative) are generally preferred, indicating a model that better captures the underlying data structure with fewer parameters. Lastly, the model's goodness of fit was assessed using the chi-square test. A non-significant chi-square value suggests that the observed and expected covariances are not substantially different, indicating a suitable model fit.

Finally, items were selected in such a way as to preserve the theoretical structure in order to ensure the content validity of the test. For EFA, a factor loading greater than 0.4 was considered necessary for the item's inclusion in each factor (74).

An additional measure to assess the appropriateness of the proposed factorial solution involved the use of alternative models (1, 2, 3 factors). For this purpose, fit measures, and the percentage of explained variance were analysed. Furthermore, the distribution of factors and their respective factorial weights will be presented.

2.3.2 Floor and ceiling effect

The floor and ceiling effect were evaluated by calculating the percentage of patients who obtained the minimum or maximum possible scores. If at least 15% of the patients achieved the minimum/maximum score, a floor/ceiling effect was considered to be present (75).

2.3.3 Concurrent validity

The concurrent validity was measured using Pearson correlations between BioPMovQ and the other disability and psychological measures. A value <0.30 was considered a low correlation, 0.30–0.60 a moderate correlation and > 0.60 a strong correlation (75).

1 Disability. Disability was assessed with the Spanish version of the GCPS, which has been employed to measure the degree of interference from chronic pain in activities of daily living. The GCPS consists of 8 items with response options in 11-point Likert format, with a total range of 0–70 points. The scale has 2 sub-scales, one measuring pain intensity and the other disability, and grades disability into moderate and severe levels. The Spanish version of this scale has demonstrated good internal consistency (Cronbach α, 0.87) (40).

2 Pain intensity. Self-reported pain intensity was assessed with the NPRS (0–10/10). On this scale, a score of 0 indicates "no pain" while a score of 10 indicates "maximum possible pain intensity" (76).

3 Pain catastrophism. To measure the level of pain catastrophising, we employed the Spanish version of the PCS, which has demonstrated adequate internal consistency (Cronbach's α, 0.79) and test–retest reliability (ICC, 0.84) (77). The scale contains 13 items subdivided into 3 domains: rumination (constant worry and inability to inhibit pain-related thoughts, 4 items), magnification (exaggeration of the unpleasantness of pain, 3 items), and hopelessness (loss of hope for achieving something or for some physical and/or psychological aspect detrimental to health to disappear, 6 items) (77).

4 Chronic pain self-efficacy. The level of self-efficacy was assessed using the Spanish version of the CPSS, which has acceptable psychometric properties for assessing perceived self-efficacy and the ability to cope with the consequences of chronic pain (Cronbach's α, 0.91) (78). The version consists of 19 items subdivided into 3 dimensions: self-efficacy in coping with symptom control, self-efficacy in pain management and self-efficacy in physical function. The final score ranges from 0 to 190, and the total score is obtained with the sum of the 3 dimensions, with higher scores indicating higher self-efficacy (48).

5 Fear of movement. To measure fear of movement, we employed the Spanish version of the TSK-11, which has adequate psychometric properties and good internal consistency (Cronbach's α, 0.81) (42). The scale consists of 2 subscales, one related to fear of physical activity and the other related to fear of harm. Each of the 11 items was scored from 1–4 (1 = "strongly disagree," 2 = "disagree," 3 = "agree," 4 = "strongly agree"), for total scores ranging from 11 to 44, with higher scores indicating greater fear of movement (42).

2.3.4 Reliability

Internal consistency was measured with Cronbach's α and item-total correlation coefficients. The internal consistency was considered appropriate when the α coefficient was ≥0.70 (79). We also computed McDonald's coefficient ω (total) using the psych R package (73). This is one index recommended as an alternative to Cronbach's α (80).

We examined the test–retest reliability using the ICC and considered that values <0.50 indicated poor reliability, 0.50–0.75 indicated moderate reliability, 0.75–0.90 indicated good reliability and > 0.90 indicated excellent reliability (81).

Measurement error was expressed as a standard error of the mean (SEM), which was calculated using the formula $SEM = SD * \sqrt{(1 - ICC)}$, in which SD is the standard deviation of the values from all participants (82, 83).

The minimum detectable change (MDC) was calculated to establish whether the magnitude of change observed between the 2 measures (separated by 7–8 days) reflected real change and not just measurement error. The MDC at the 95% confidence interval (MDC_{95}) was calculated as $SEM \times 2^{-} \sqrt{} \times 1.96$ (82).

2.3.5 Discriminant validity

Discriminant validity analysis of the BioPMovQ was employed to assess varying degrees of pain-related motor and functional impairment. As a criterion variable, the disability sub-scale from the GCPS was utilised, which gauges the extent of pain interference on daily activities. Scores ranging from 17 to 24 are classified as moderately limiting interference, while those from 25 to 40 indicate severely limiting interference. In this analysis, we will classify the participants into subclinical, moderate, and severe levels of pain-related motor and functional impairment.

The Kruskal-Wallis H test and the Mann–Whitney test were applied to discern differences between the levels of motor and functional impairment linked to pain. Furthermore, the area under the receiver operating characteristic curve was evaluated to determine the proportion of patients accurately classified across different levels. The highest value for this metric is 1, indicating optimal diagnostic utility. Diagnostic accuracy is deemed excellent for values ranging from 0.9 to 1, very good for 0.8 to 0.9, good for 0.7 to 0.8, fair for 0.6 to 0.7, and poor for 0.5 to 0.6. Any value below 0.5 renders the test non-informative (84). The optimal cutoff point between levels of motor and functional impairment associated with pain was determined using the Youden index (85). Additionally, for each score, diagnostic test indicators such as sensitivity, specificity, negative predictive value, and positive predictive value were calculated.

3 Results

3.1 Content validity analysis

In the expert analysis of the content, 2 items were eliminated ("a. Physical activity can be counterproductive for my problem" and "b. Did cardiovascular exercise such as walking or cycling to reduce my pain") because the score according to Aiken's V was <0.70, and there were numerous comments questioning the specificity and usefulness of these items.

A total of 25 items were validated, with a range of 0.70–0.95 according to Aiken's V. All theoretical constructs were validated by the expert committee.

Table 1 shows the Aiken V values for each item, the theoretical constructs and the general comments of the expert committee.

3.2 Characteristics of the sample

The total sample consisted of 200 participants with chronic musculoskeletal pain, 68.6% of whom were women. Table 2 presents the patients' sociodemographic characteristics and scores on the various self-reported scales. The BioPMovQ data did not follow a normal distribution, but the instrument's response rate was 100%. In Table 3, the descriptive statistics for each item of the BioPMovQ are presented, along with the 'if item dropped' metrics such as Item, Mean, SD, Skewness, Kurtosis, frequencies for 0 to 4, Item-rest correlation, Cronbach's α, and McDonald's ω.

3.3 Exploratory factor analysis

Item statistics are presented in the Table 3. It can be seen how all items contribute to internal consistency and that skewness and kurtosis generally remain below 2. The KMO test showed an acceptable data suite for factor analysis (KMO score of 0.829), there were no multicollinearity problems, and Bartlett's test of sphericity rejected the identity matrix null hypothesis (χ^2 (120) = 869.88, $p < 0.001$).

Based on these results, continuing with the EFA would be justified. Lastly, we used the generalised least squares method of factor extraction with oblimin rotation. The semi-confirmatory parallel analysis recommended between 3 and 5 factors, although the EGA analysis with 500 bootstrap iterations showed that the most repeated solutions were those with 3 to 5 factors (with proportions of 0.324, 0.376, 0.184, respectively). For theoretical reasons and in order to cover all relevant areas described in developing items section finally present a four-factor solution. The four-factor model of the BioPMovQ exhibited a favourable fit as indicated by the model fit metrics: χ^2 (62) = 74.6, $p = 0.131$; BIC = −254; TLI = 0.967; RMSEA = 0.031 with a 95% confidence interval of 0.001–0.055.

The four-factor solution which together represented 55.79% of the total variance. The first factor (28.85% of the total variance) consisted of 4 items. The theoretical content of this factor was labelled "disability." The second factor (13.55% of the total variance) consisted of 4 items and referred to self-efficacy for physical activity. The third factor ("movement fear-avoidance beliefs and behaviours") included 3 items and accounted for 6.84% of the total variance. The fourth factor ("self-perception of functional ability") presented 4 items and

10.3389/fmed.2024.1358829

TABLE 1 Aiken V values for each item, the theoretical constructs and the general comments of the expert committee.

Content analysis by expert judges (n = 11)				
Theoretical factors and items	Relevance	Comprehensiveness	Comprehensibility	Comments
TF. Movement avoidance behaviours	0.9 (0.71 to 0.97)	1 (0.83 to 1)	0.95 (0.76 to 0.99)	
The pain increases if I perform more movements during the day	0.75 (0.53 to 0.88)	0.7 (0.48 to 0.85)	0.8 (0.58 to 0.91)	Reviewer 3. This can be an avoidance belief or an experience
Certain movements worsen my problem, and I avoid making them	0.9 (0.71 to 0.97)	0.95 (0.76 to 0.99)	0.85 (0.64 to 0.95)	Reviewer 7. This item appears to be redundant considering the previous one
Physical activity can be counterproductive for my problem	0.7 (0.48 to 0.85)	0.6 (0.38 to 0.78)	0.55 (0.34 to 0.88)	Reviewer 2, 4. Redundancy Reviewer 6. The word "problem" is very general, and the patients might not relate it to the pain specifically
The less I move the area that hurts, the better I will recover	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	0.9 (0.71 to 0.97)	
I avoid performing certain movements that can injure me	0.85 (0.64 to 0.95)	0.95 (0.76 to 0.99)	0.9 (0.71 to 0.97)	
My work activity worsens my pain	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	0.85 (0.64 to 0.95)	Revisor 10. I do not consider this is an avoidance belief
TF. Self-efficacy for physical activity	1 (0.83 to 1)	1 (0.83 to 1)	1 (0.83 to 1)	
I can perform a therapeutic exercise programme to reduce the pain	0.9 (0.71 to 0.97)	0.95 (0.76 to 0.99)	0.9 (0.71 to 0.97)	
I can perform a therapeutic exercise programme, although the symptoms increase slightly	0.95 (0.76 to 0.99)	0.95 (0.76 to 0.99)	1 (0.83 to 1)	
I can perform daily life activities that are physical demanding	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	0.85 (0.64 to 0.95)	Reviewer 1. There are many types of daily life activities. It might be interesting to add some examples
I can perform a physical exercise programme despite fatigue symptoms appearing	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	0.75 (0.53 to 0.88)	Reviewer 8, 9. Redundancy
I can perform work activities that are physical demanding	0.9 (0.71 to 0.97)	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	
TF. Physical discomfort	0.9 (0.71 to 0.97)	0.9 (0.71 to 0.97)	0.95 (0.76 to 0.99)	Reviewer 5. There are several items in this factor that could be in the section of avoidance beliefs and behaviours
When I have pain, I avoid moving to feel better	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	0.85 (0.64 to 0.95)	
When I have pain, I lie down to try to make the pain go away	0.95 (0.76 to 0.99)	0.95 (0.76 to 0.99)	0.9 (0.71 to 0.97)	
Due to the pain, the movements I make are uncoordinated and lack fluidity	1 (0.83 to 1)	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	
I try recreational physical activities to distract myself from the pain	0.75 (0.53 to 0.88)	0.7 (0.48 to 0.85)	0.75 (0.53 to 0.88)	Reviewer 8. Only a small group of patients would be reflected in this item.

(Continued)

TABLE 1 (Continued)

Content analysis by expert judges ($n = 11$)				
Theoretical factors and items	Relevance	Comprehensiveness	Comprehensibility	Comments
I perform body movements to reduce the pain	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	0.85 (0.64 to 0.95)	
I perform cardiovascular exercises such as walking and cycling to reduce my pain	0.55 (0.34 to 0.74)	0.6 (0.38 to 0.78)	0.7 (0.48 to 0.85)	Reviewer 9. This is highly technical, difficult-to-understand language. Reviewer 4. This item is not very generalizable. Reviewer 8. Only a small group of patients would be reflected in this item.
The pain stops me from maintaining a comfortable posture, and I have to constantly change position	0.8 (0.58 to 0.91)	0.7 (0.48 to 0.85)	0.75 (0.53 to 0.88)	
TF. Self-perceived functional ability	0.95 (0.76 to 0.99)	1 (0.83 to 1)	0.95 (0.76 to 0.99)	
My daily life activities tire me out	0.9 (0.71 to 0.97)	0.95 (0.76 to 0.99)	0.85 (0.64 to 0.95)	
My muscles are tense (rigid) and lack flexibility	0.7 (0.48 to 0.85)	0.85 (0.64 to 0.95)	0.85 (0.64 to 0.95)	Reviewer 3. This item does not correspond to the functional capacity concept
The movements I make are uncoordinated and jerky	0.9 (0.71 to 0.97)	0.95 (0.76 to 0.99)	0.9 (0.71 to 0.97)	
I have little strength or muscle resistance	1 (0.83 to 1)	1 (0.83 to 1)	1 (0.83 to 1)	
I have difficulty performing movements that require a lot of precision such as grasping, manipulating, or cutting objects.	0.9 (0.71 to 0.97)	0.95 (0.76 to 0.99)	0.9 (0.71 to 0.97)	
TF. Disability	1 (0.83 to 1)	1 (0.83 to 1)	1 (0.83 to 1)	Reviewer 11. It appears to me that this factor evaluates the interference of pain in activities more than the disability construct
The pain stops me from adequately performing my work activity	0.8 (0.58 to 0.91)	0.85 (0.64 to 0.95)	0.85 (0.64 to 0.95)	
The pain stops me from adequately performing my household chores	0.75 (0.53 to 0.88)	0.7 (0.48 to 0.85)	0.85 (0.64 to 0.95)	
The pain has decreased or halted my recreational and societal activities	0.95 (0.76 to 0.99)	0.9 (0.71 to 0.97)	0.85 (0.64 to 0.95)	
The pain stops me from performing physical and sport activities	0.8 (0.58 to 0.91)	0.7 (0.48 to 0.85)	0.85 (0.64 to 0.95)	

TF, Theoretical factors.

accounted for 6.82% of the total variance. The factor loadings for each item are shown in Table 4. A total of 7 items were eliminated because the factorial weight was <0.40.

The alternative models analysed do not offer a suitable factorial solution, as their fit metrics are not acceptable. Additionally, several items exhibit factorial weights below 0.40, and the percentage of variance explained by each of these alternative models is significantly lower than that of the proposed factorial solution (Tables 5, 6).

There was no floor or ceiling effect. Two patients scored 18 points, which is the minimum possible (0.01%), and only 1 patient scored the maximum (0.001%/72 points).

TABLE 2 Sociodemographic and clinical data and scores obtained on the self-reported scale.

Sociodemographic and clinical data	Mean ± SD	Range (Min-Max)
Age (years)	48.87 ± 14.75	19–82
BDI (kg/m^2)	25.66 ± 4.61	17.36–39.45
BioPMovQ	38.36 ± 11.07	14–64
Pain duration (months)	35.12 ± 34.02	6–156
Self-efficacy for physical activity	7.43 ± 3.51	1–16
Disability	10.04 ± 4.07	1–16
Movement fear-avoidance beliefs and behaviours	9.15 ± 2.85	1–12
Self-perceived functional ability	11.62 ± 4.94	1–20
TSK-11	27.51 ± 7.64	12–44
TSK harm	12.05 ± 4.87	3–28
TSK activity avoidance	15.53 ± 5.25	4–28
PCS	15.37 ± 10.43	1–45
PCS rumination	5.54 ± 3.97	0–16
PCS magnification	3.37 ± 2.53	0–12
PCS helplessness	6.47 ± 5.02	1–20
CPSS	137.83 ± 33.1	28–190
PSE	57.22 ± 14.34	9–80
SSE	30.81 ± 12.36	0–50
FSE	49.74 ± 11.91	8–60
GCPS	36.98 ± 13.95	6–63
GCPS pain intensity	19.41 ± 4.66	4–30
GCPS disability	17.70 ± 10.92	0–40
Numerical pain rating scale	6.52 ± 1.66	3–10
Categorical variables	n (%)	
Gender		
Women	153 (68.6)	
Men	47 (21.1)	
Employment status		
Employed	120 (53.8)	
Unemployed	18 (8.1)	
Medical leave due to disability	27 (12.1)	
Retired	35 (15.7)	
Level of Education		
Uneducated	3 (1.3)	
Primary education	26 (11.7)	
Secondary education	82 (36.8)	
University education	89 (39.9)	

BDI, Body mass index; BioPMovQ, Biobehavioural Pain and Movement Questionnaire; TSK-11, Tampa Scale of Kinesiophobia; PCS, Pain Catastrophising Scale; CPSS, Chronic Pain Self-Efficacy Scale; GCPS, Graded Chronic Pain Scale; PSE, self-efficacy in pain management; SSE, self-efficacy in coping with symptom control; FSE, self-efficacy in physical function; SD, standard deviation.

3.4 Concurrent validity

Overall, the BioPMovQ total score presented moderate magnitude correlations with most of the psychological and disability variables. With respect to the BioPMovQ subscales, the correlations were small to moderate in magnitude. Table 7 shows the correlations between the BioPMovQ and its subscales with all the assessed self-reported scales.

3.5 Reliability

The internal consistency of the BioPMovQ was Cronbach's Alpha = 0.82 and McDonald's $\omega = 0.83$, with its 4 subscales showing an internal consistency of 0.64–0.75. To assess the instrument's test–retest reliability, 51 patients (74.5% women; age, 47.74 ± 14.71 years) re-took the scale 10.13 ± 12.52 days later. According to the ICC, the scale's stability over time was excellent, with an MDC_{95} of 9.50. Table 8 shows

TABLE 3 Descriptive statistics.

											if item dropped	
Item	Mean	SD	Skewness	Kurtosis	Freq. 0	Freq. 1	Freq. 2	Freq. 3	Freq. 4	Item-rest correlation	Cronbach's α	McDonald's ω
1	2.97	1.27	−1.17	0.24	0.09	0.08	0.08	0.31	0.46	0.43	0.83	0.84
2	1.82	1.18	0.55	−0.57	0.10	0.38	0.30	0.09	0.15	0.31	0.84	0.84
3	2.45	1.34	−0.41	−1.08	0.10	0.19	0.15	0.29	0.28	0.45	0.83	0.84
4	1.80	1.30	0.38	−1.09	0.15	0.39	0.14	0.19	0.15	0.31	0.84	0.84
5	2.45	1.38	−0.40	−1.23	0.10	0.23	0.09	0.30	0.29	0.50	0.83	0.83
6	3.20	1.16	−1.55	1.49	0.06	0.06	0.07	0.27	0.56	0.49	0.83	0.84
7	1.83	1.12	0.44	−0.40	0.10	0.33	0.36	0.11	0.12	0.20	0.84	0.85
8	2.12	1.45	−0.03	−1.43	0.17	0.26	0.13	0.20	0.25	0.29	0.84	0.84
9	2.88	1.34	−1.10	−0.04	0.12	0.07	0.08	0.31	0.43	0.33	0.84	0.84
10	2.41	1.36	−0.44	−1.12	0.12	0.19	0.11	0.33	0.26	0.55	0.83	0.83
11	1.71	1.39	0.36	−1.26	0.22	0.35	0.08	0.21	0.15	0.36	0.84	0.84
12	1.95	1.09	0.31	−0.61	0.07	0.32	0.34	0.18	0.11	0.22	0.84	0.84
13	3.26	1.14	−1.73	2.13	0.06	0.06	0.03	0.29	0.57	0.31	0.84	0.84
14	3.06	1.28	−1.38	0.74	0.10	0.06	0.05	0.30	0.51	0.46	0.83	0.84
15	2.81	1.35	−0.78	−0.80	0.07	0.18	0.06	0.26	0.44	0.46	0.83	0.84
16	1.55	1.38	0.57	−0.97	0.27	0.34	0.12	0.13	0.15	0.25	0.84	0.85
17	1.81	1.09	0.37	−0.47	0.10	0.34	0.33	0.15	0.09	0.31	0.84	0.84
18	1.70	1.44	0.33	−1.21	0.28	0.22	0.20	0.13	0.18	0.35	0.84	0.84
19	2.09	1.46	−0.16	−1.45	0.20	0.22	0.07	0.31	0.20	0.57	0.83	0.83
20	2.99	1.31	−1.22	0.21	0.09	0.10	0.02	0.32	0.48	0.50	0.83	0.84
21	1.89	1.28	0.29	−0.92	0.14	0.29	0.28	0.13	0.17	0.26	0.84	0.84
22	1.98	1.11	0.49	−0.43	0.06	0.30	0.41	0.08	0.16	0.44	0.84	0.84
23	2.55	1.46	−0.60	−1.10	0.15	0.15	0.09	0.27	0.36	0.57	0.83	0.83
24	2.39	1.54	−0.42	−1.38	0.19	0.15	0.09	0.23	0.35	0.31	0.84	0.84
25	2.21	1.50	−0.23	−1.44	0.20	0.19	0.11	0.25	0.27	0.48	0.83	0.84

SD, standard deviation.

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TABLE 4 Observational factor analysis.

	Disability	Self-efficacy for physical activity	Movement avoidance behaviours	Self-perceived functional ability
5. The pain stops me from adequately performing my work activity	**0.84**			0.40
10. The pain stops me from adequately performing my household chores	**0.68**		0.44	0.39
24. The pain has decreased or halted my recreational and societal activities	**0.49**			
15. The pain stops me from performing physical and sport activities	**0.44**		0.35	0.41
2. I can perform a therapeutic exercise programme to reduce the pain		**0.73**		
22. I can perform work activities that are physical demanding		**0.67**		
17. I can perform a physical exercise programme despite fatigue symptoms appearing		**0.66**		
12. I can perform daily life activities that are physical demanding		**0.59**		
6. Certain movements worsen my problem, and I avoid making them	0.37		**0.90**	0.42
20. I avoid performing certain movements that can injure me	0.40		**0.47**	0.45
1. The pain increases if I perform more movements during the day			**0.45**	0.39
23. I have little strength or muscle resistance	0.60			**0.72**
25. I have difficulty performing movements that require a lot of precision such as grasping, manipulating, or cutting objects.	0.34			**0.70**
19. I have difficulty performing daily life activities such as walking fast or climbing stairs	0.41			**0.67**
14. My muscles are tense (rigid) and lack flexibility			0.37	**0.51**
11. My daily life activities tire me out				**0.45**

Method-GLS_Oblimin. Bold values indicate factor analysis results >0.40.

TABLE 5 Comparations fit measures for factor models.

		RMSEA 90% CI				Model test			
Model	RMSEA	Lower	Upper	TLI	BIC	χ^2	df	*p*	% of variance
4 Factors	0.031	0.001	0.055	0.967	−254	74.6	62	0.131	55.79%
3 Factors	0.056	0.038	0.074	0.895	−274	124	75	<0.001	48.9%
2 Factors	0.066	0.051	0.082	0.857	−303	168	89	<0.001	42.12%
1 Factors	0.106	0.093	0.119	0.639	−213	338	104	<0.001	28.57

RMSEA, Root Mean Square Error of Approximation; CI, Confidence Interval; TLI, Tucker-Lewis Index; BIC, Bayesian Information Criterion; χ^2, Chi-squared Test; df, Degrees of Freedom; % of Variance, Percentage of Variance Explained; 90% CI, 90% confidence interval.

the descriptive statistics and results of the test–retest reliability and responsiveness analysis for the BioPMovQ and its subscales. The highest correlations with the other instruments of the global scale were presented with the GCPS and the TSK-11 and were lower with the NPRS.

3.6 Discriminant validity

Utilizing the Kruskal-Wallis test, significant differences in BioPMovQ were observed among levels of pain-related motor and functional impairment ($H = 64.54$, $p < 0.001$). Subsequent Mann–Whitney tests indicated disparities between: (a) individuals subclinical and those with moderate pain-related motor and functional impairment ($U = 1340.50$, $p = 0.003$), (b) those subclinical and those with severe pain-related motor and functional impairment ($U = 706$, $p < 0.001$), and (c) moderate versus severe levels ($U = 803.50$, $p < 0.001$). The rank averages consistently reflected a pattern where the scores increased with the severity of pain-related motor and functional impairment, suggesting a clear distinction in BioPMovQ scores based on the level. In Figure 1, a violin plot representation of the various levels of the BioPMovQ based on pain-related motor and functional impairment can be observed.

The BioPMovQ demonstrated robust diagnostic precision in discerning patients at the severe level, evidenced by high specificity and sensitivity. In terms of the moderate level, sensitivity was

TABLE 6 Factorial structure using alternative models to the proposed factorial structure.

	1 Factor Model	2 Factors Model		3 Factors Model		
	1	1	2	1	2	3
5. The pain stops me from adequately performing my work activity	0.63	0.68		0.71		
10. The pain stops me from adequately performing my household chores	0.65	0.66		0.63		
24. The pain has decreased or halted my recreational and societal activities	0.37**	0.42		0.46		
15. The pain stops me from performing physical and sport activities	0.51	0.52		0.49		
2. I can perform a therapeutic exercise programme to reduce the pain	0.33**	0.21**			0.71	
22. I can perform work activities that are physical demanding	0.38**	0.27**			0.67	
17. I can perform a physical exercise programme despite fatigue symptoms appearing	0.26**	0.14**			0.67	
12. I can perform daily life activities that are physical demanding	0.18**		0.58		0.58	
6. Certain movements worsen my problem, and I avoid making them	0.57	0.58				0.922
20. I avoid performing certain movements that can injure me	0.55	0.55				0.49
1. The pain increases if I perform more movements during the day	0.47	0.45				0.45
23. I have little strength or muscle resistance	0.71	0.72				0.33**
25. I have difficulty performing movements that require a lot of precision such as grasping, manipulating, or cutting objects.	0.55	0.55		0.56		
19. I have difficulty performing daily life activities such as walking fast or climbing stairs	0.62	0.60		0.61		
14. My muscles are tense (rigid) and lack flexibility	0.48	0.47		0.43		–
11. My daily life activities tire me out	0.41	0.40		0.40		

**Items recommended for removal due to factor loadings below 0.40.

TABLE 7 Concurrent validity of the BioPMovQ.

Concurrent validity	BioPMovQ				
	Total score	Disability	Self-efficacy for physical activity	Movement avoidance behaviours	Self-perceived functional ability
GCPS	**0.52	**0.55	**0.27	**0.39	**0.38
GCPS disability	**0.51	**0.54	**0.28	**0.34	**0.35
GCPS pain intensity	**0.44	**0.40	*0.17	**0.38	**0.33
NPRS	**0.31	*0.17	*0.15	**0.28	**0.26
TSK-11	**0.60	**0.45	**0.22	**0.53	**0.54
TSK harm	**0.51	**0.25	**0.51	**0.32	**0.38
TSK activity avoidance	**0.32	**0.35	*0.14	**0.34	**0.37
PCS	**0.44	**0.43	*0.18	**0.32	**0.38
PCS rumination	**0.39	**0.37	**0.22	**0.28	**0.33
PCS magnification	**0.32	**0.31	**0.16	**0.24	**0.26
PCS helplessness	**0.42	**0.44	0.13	**0.31	**0.39
CPSS	**−0.31	**−0.32	**−0.44	**−0.22	**−0.21
PSE	**−0.26	**−0.27	**−0.37	**−0.19	**−0.19
SSE	**−0.26	**−0.29	**−0.40	**−0.21	**−0.18
FSE	**−0.27	**−0.25	**−0.34	*−0.16	**−0.18

BioPMovQ, Biobehavioural Pain and Movement Questionnaire; NPRS, Numerical Pain Rating Scale; TSK, Tampa Scale of Kinesiophobia; PCS, Pain Catastrophising Scale; CPSS, Chronic Pain Self-Efficacy Scale; PSE, self-efficacy in pain management; SSE, self-efficacy in coping with symptom control; FSE, self-efficacy in physical function; GCPS, Graded Chronic Pain Scale.

satisfactory, while specificity was commendable. Table 9 delineates the diagnostic precision, including the salient cut-off points. The optimal cutoffs were determined to be <37 for subclinical, ≥37 for moderate, and ≥45 for severe levels. For the moderate level, sensitivity was 0.87 with a 95% CI of [0.76–0.84], while specificity stood at 0.59 with a 95% CI of [0.44–0.62]. For the severe level, sensitivity and specificity were

TABLE 8 Reliability analysis.

	McDonald's ω	Cronbach's alpha	Mean ± SD		ICC (95% CI)	SEM	MDC_{90}	MDC_{95}
			Test 1	Test 2				
BioPMovQ	0.83	0.82	36.06 ± 10.7	38.16 ± 8.03	0.86 (0.76 to 0.91)	3.43	8.04	9.50
Disability	0.71	0.70	9.54 ± 4	10.26 ± 3.55	0.86 (0.77 to 0.91)	1.41	3.29	3.91
Self-efficacy for physical activity	0.75	0.75	6.16 ± 2.67	6.88 ± 2.33	0.88 (0.80 to 0.93)	0.87	2.03	2.41
Movement fear-avoidance beliefs	0.65	0.64	8.54 ± 3.27	8.69 ± 2.95	0.86 (0.77 to 0.91)	1.16	2.71	3.22
Self-perceived functional ability	0.74	0.73	11.56 ± 4.33	12.26 ± 3.23	0.83 (0.72 to 0.90)	1.58	3.68	4.37

BioPMovQ, Biobehavioural Pain and Movement Questionnaire; SD, standard deviation; ICC, intraclass correlation coefficient; MDC_{90}, minimal detectable change at the 90% confidence level; MDC_{95}, minimal detectable change at the 95% confidence level; SEM, standard error of the mean.

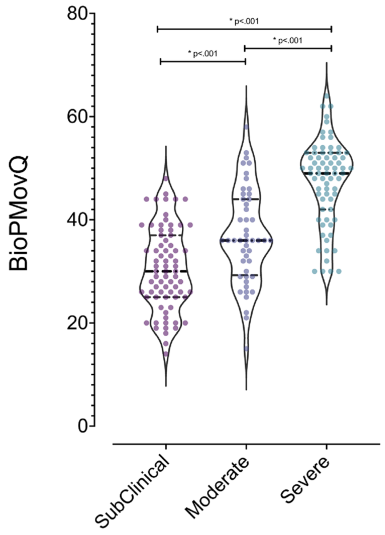

FIGURE 1
Differences in functional and motor alterations levels related to pain as measured by the BioPMovQ. *Indicates statistical significance (p<.001) and the 95% confidence interval considered for comparisons between variables using the Mann–Whitney U test.

0.72 ([0.61–0.82]) and 0.98 ([0.92–1]), respectively. Figures 2, 3 further elucidate these findings. To determine the optimal cut-off points and conduct sensitivity and specificity analyses, the R package named OptimalCutpoints was used (86).

4 Discussion

The BioPMovQ is an instrument designed to assess (from a biobehavioural perspective) pain related to functional and motor impairments in patients with musculoskeletal pain. This study provides evidence on the psychometric properties of the BioPMovQ, including its content validity, factor analysis, internal consistency, test–retest reliability and concurrent validity, which suggest that this instrument meets the recommended minimum standards for patient-centered measures proposed by the International Society for Quality of Life Research (87). Overall, the findings of this research show that the BioPMovQ has adequate psychometric properties, showing good validity and reliability for the assessment of the designed construct.

The results of the study indicate that the BioPMovQ has good content validity as assessed by experts, indicating that the questions in the questionnaire have adequate relevance, completeness and comprehensibility and are suitable for measuring the construct of pain related to functional and motor impairments from a biobehavioural perspective in the population with musculoskeletal pain. The BioPMovQ also met the criteria proposed by Patrick et al. (88) for determining good content validity: a correct qualitative phase of instrument development and construction and evidence that identifies adequate understanding of the instrument (88). In the content analysis phase, the experts validated 5 theoretical sub-constructs of the initial instrument; in the exploratory factor analysis, they obtained a 4-factor solution that together accounted for 55.79% of the total variance. The values obtained in the KMO index indicate that the instrument has a good level of multicollinearity between items (89). Each of the subscales had 3–5 items, as recommended by a number of authors (89). The factor loadings of 17 of the 18 items were ≥ 0.44, which are considered strong (74), increasing the solidity of the obtained factor structure. Another positive aspect is that a 5-point Likert scale was employed, which is a good option when the data follow a normal distribution, as in our case (67).

Lastly, the following 4 factors or subscales were included: disability; self-efficacy for physical activity; movement avoidance behaviours; self-perceived functional ability. For 2 of the factors, however, the initial theoretical name had to be redefined, possibly because 7 items were eliminated during the exploratory factor analysis, and 3 items were distributed differently from the initial theoretical assumption.

The BioPMovQ has been designed and constructed from a biobehavioural perspective, which implies that the biological, psychological (affective, cognitive) and social aspects are interrelated (90), thereby providing a broader view in understanding the impact of pain on movement and function in patients with chronic musculoskeletal pain. It makes sense to employ global scoring for decision making using the biobehavioural paradigm.

With its various subscales, the BioPMovQ provides an innovative and comprehensive clinical assessment, with 4 measured factors that can be considered determinants for the functional approach to patients with chronic pain, for which other instruments are not

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TABLE 9 Diagnostic accuracy results and all optimal cut-off points of BioPMovQ.

	Subclinical	Moderate	Severe
Mean ± SD	30.73 ± 8.03	36.85 ± 9.27	47.49 ± 8.15
95% CI	[28.91–32.54]	[34.16–39.86]	[45.56–49.42]
Median (25th percentile; 75th percentile)	30 (P25 = 25; P75 = 38)	36 (P25 = 29.25; P75 = 44)	49 (P25 = 42; P75 = 53)
Cases, N (%)	78 (39.59%)	48 (24.37%)	71 (36.04%)
Optimal cuff-off point	<37	≥37	≥45
Sensitivity (95% CI)	–	0.87 [0.76–0.84]	0.72 [0.61–0.82]
Specificity (95% CI)	–	0.59 [0.44–0.62]	0.98 [0.92–1]
Positive predictive value (95% CI)	–	0.73 [0.61–0.75]	0.98 [0.90–0.98]
Negative predictive value (95% CI)	–	0.78 [0.62–0.74]	0.78 [0.68–0.99]

SD, standard deviation; 95% CI, confidence interval.

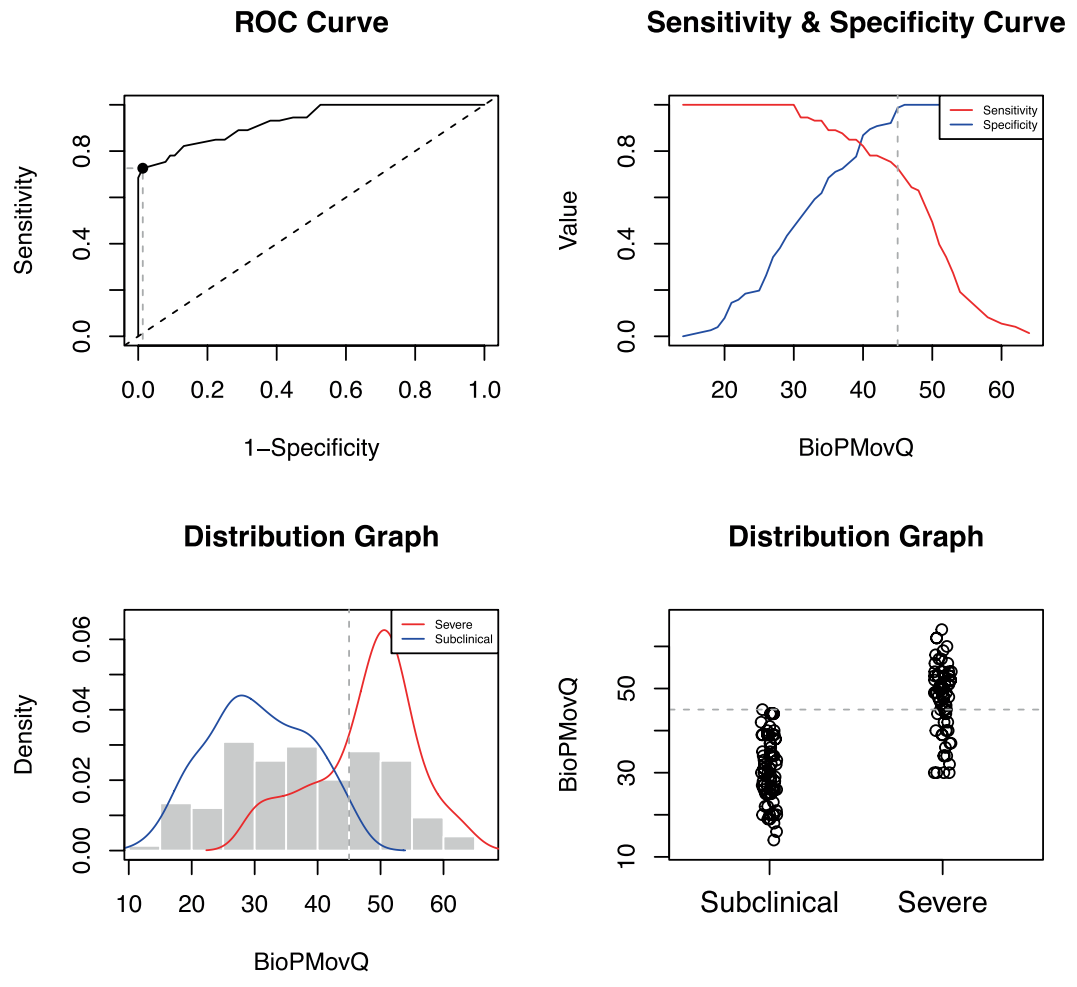

FIGURE 2
Optimal cut-off point between levels of BioPMovQ (Subclinical vs. Severe). A ROC (receiver operating characteristic) curve that represents the sensitivity of a diagnostic test that produces continuous results, depending on false positives (complementary to specificity), for different cut-off points, the image where the cut-off point at which the highest sensitivity and specificity is achieved and finally, a subclinical and moderate sample distribution graph.

currently integrated into a single construct. The physical activity self-efficacy subscale assesses the patient's confidence in their ability to perform physical activities despite pain. The disability subscale assesses the impact of pain on the performance of work and daily living activities. The movement avoidance behaviour subscale assesses the individual's tendency to avoid certain activities due to pain. The self-perceived functional ability subscale assesses the individual's ability to perform specific tasks related to physical exertion.

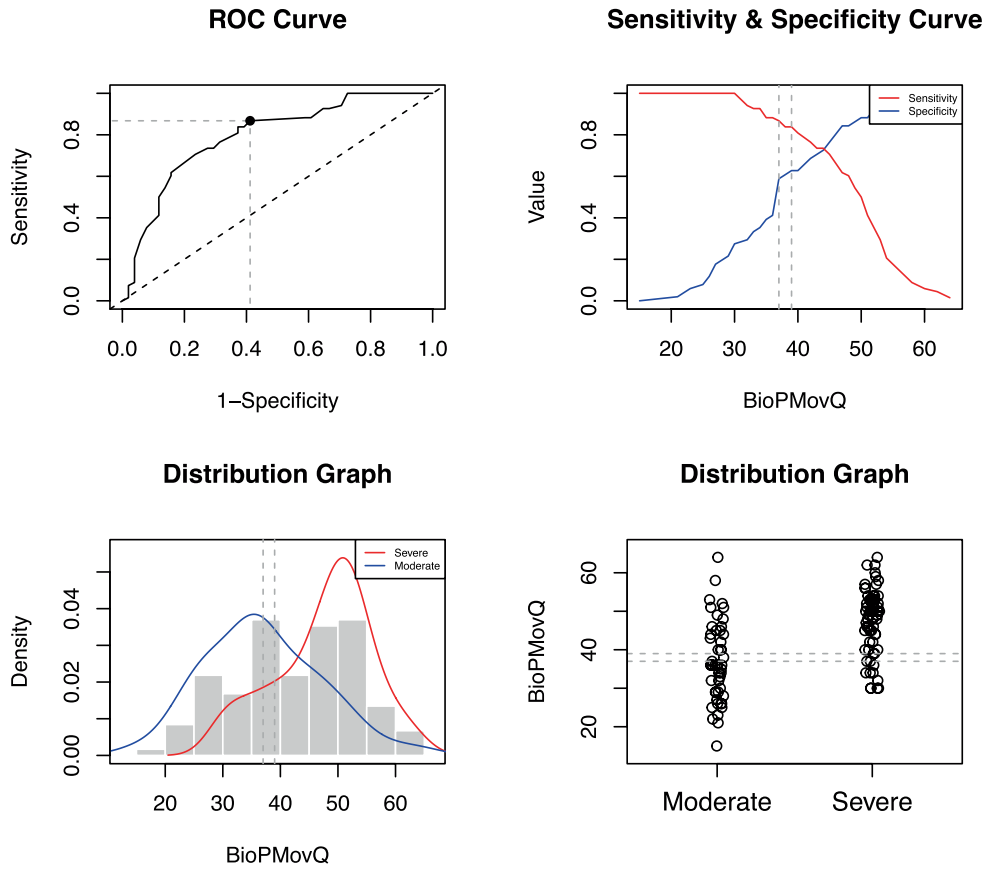

FIGURE 3
Optimal cut-off point between levels of BioPMovQ (Moderate vs. Severe). A ROC (receiver operating characteristic) curve that represents the sensitivity of a diagnostic test that produces continuous results, depending on false positives (complementary to specificity), for different cut-off points, the image where the cut-off point at which the highest sensitivity and specificity is achieved and finally, a subclinical and moderate sample distribution graph.

Findings related to concurrent validity show that the BioPMovQ presents low/moderate correlations with instruments measuring chronic pain self-efficacy, pain catastrophising, pain intensity, disability and kinesiophobia, the latter 2 correlations being the highest recorded ($r = 0.52$ and $r = 0.60$, respectively). These results describe possible relationships with other constructs but also demonstrate that the BioPMovQ and its subscales measure different aspects and rule out the possibility that the instrument is repetitive or redundant with respect to other instruments. The internal consistency of the BioPMovQ was good (Cronbach's $\alpha = 0.82$; McDonald's $\omega = 0.83$); that of most of the subscales was also acceptable (Cronbach's α, >0.70), except for the subscale of avoidance motor behaviours (Cronbach's α, 0.64), which were poor. This subscale includes only 3 items was the shortest subscale and that could have affected internal consistency.

The test–retest reliability of the BioPMovQ was good (ICC of 0.86), as were those of all the subscales (ICC > 0.83). A mean of separation of 10.13 ± 12.52 days between the 2 measurements was employed to prevent patients from recalling their previous responses and avoid strong fluctuations in their clinical status. This period was adequate, considering that a period of 2–14 days between measurements is considered acceptable for assessing test–retest reliability (91). Considering the BioPMovQ's total score, the SEM and the MDC_{90} presented relatively low values (3.43 and 8.04, respectively), a relevant aspect given that the purpose of the MDC is to detect real changes that are outside the measurement error (92), with smaller results indirectly indicating that the measure is stable in repeated measurements over time.

As for the floor/ceiling effect, only 2 patients (0.01%) obtained the minimum score, while 1 patient (0.001%) obtained the maximum score, which indicates an absence of the floor/ceiling effect (75). The 100% BioPMovQ response rate could have been due to several reasons, including the rigorous process employed for developing the items and the adequate understanding demonstrated in the pilot test with patients. Another factor to consider is the instrument's brevity. Other authors have reported an association between the questionnaire's high response rate and length, given that longer questionnaires have lower response rates (93).

4.1 Clinical implications

The introduction of the BioPMovQ represents a significant advancement in the assessment and management of chronic musculoskeletal pain from a biobehavioural perspective. This psychometrically validated tool offers a comprehensive approach to understanding how pain impacts patient functionality and motor behaviour, acknowledging the interplay of biological, psychological, and social factors.

To our knowledge, this is the first instrument developed and psychometrically validated to assess the construct of pain related to functional and motor impairment from a biobehavioural perspective, integrating 4 subscales, 3 of which (self-efficacy for physical activity, disability, movement avoidance behaviours) already have instruments assessing similar constructs. Self-perceived functional ability have not however been sufficiently reported in the literature on chronic musculoskeletal pain, highlighting one the major advantages of the BioPMovQ: the integration of several sub-constructs into a short questionnaire, an important advantage for its clinical use in patients with chronic musculoskeletal pain, given its a broad view of pain-related functional and motor impairments. In certain contexts, the use of multiple questionnaires can be a limitation; as Vickers suggests, this can lead to excessive patient drop-out, undue burden of data management and difficulties with interpreting the results (94). In the context of musculoskeletal pain research and clinical implications, the BioPMovQ could be a solution to the overuse of self-registration.

One of the key contributions of the BioPMovQ to clinical practice is its ability to facilitate a more personalised approach to treating musculoskeletal pain. By assessing various dimensions related to pain and its influence on motor behaviour, clinicians can identify specific therapeutic targets for each patient, such as improving self-efficacy for physical activity, reducing movement avoidance behaviours, and enhancing perceived functional capacity. This customization of care aims not only to optimise therapeutic outcomes but also to improve the quality of life for patients.

Furthermore, the BioPMovQ holds potential as a valuable tool in future research on musculoskeletal pain. Its application in longitudinal studies could provide new insights into how specific therapeutic interventions, such as exercise programs or psychosocial coping strategies, affect the experience of pain and its functional consequences over time. Additionally, it could facilitate the exploration of the dynamics between biological and behavioural components of pain, paving the way for more effective biobehavioural interventions.

Another relevant clinical implication of the BioPMovQ lies in its capacity to serve as a means of communication among different healthcare professionals involved in the management of musculoskeletal pain. By providing a common language to describe the complexity of pain and its effects on mobility and functionality, it enables more effective interdisciplinary collaboration, essential for comprehensive therapeutic approaches.

4.2 Limitations and future studies

Although the BioPMovQ has demonstrated promising psychometric properties, we acknowledge several limitations that underline the need for future research. First, the current study focused on a population with chronic musculoskeletal pain. It is essential to replicate these findings in populations with acute pain conditions and across cultural contexts to validate the instrument's universality.

Secondly, while exploratory factor analysis provided a solid factorial structure for the BioPMovQ, confirmation of this structure through confirmatory factor analysis in independent samples is crucial. This step will not only reinforce the construct validity of the instrument but also its applicability across different populations and contexts.

Furthermore, item response analysis (IRT) offers an opportunity to examine the utility of each item across the construct measurement spectrum. This approach could provide valuable insights into the BioPMovQ's sensitivity to clinically meaningful changes, helping to further refine the instrument to capture crucial aspects of pain and movement from a biobehavioural perspective.

An exhaustive evaluation of the DIF and the measurement invariance of the instrument through variables such as sex remains to be done. On a tentative basis, we ran the Mantel–Haenszel procedure with purification and found that items 14, 17 and 25 appeared to be marked with DIF. It is important to verify this result in a larger sample and better balanced by sex.

A particular area of interest is the exploration of individual and group differences in responses to the BioPMovQ. Investigating measurement invariance across demographic groups, such as gender, age, and pain type, will determine if the instrument consistently interprets across diverse groups, ensuring its fairness and accuracy in measurement across different populations.

Finally, longitudinal studies employing the BioPMovQ to assess the efficacy of specific interventions, such as therapeutic exercise programs or psychosocial interventions, could provide additional evidence on the instrument's sensitivity to changes over time. This is essential for confirming the BioPMovQ's utility in monitoring treatment progress and assessing outcomes in patients with musculoskeletal pain.

5 Conclusion

This study provides evidence for the psychometric properties of the BioPMovQ. The fact that it showed good content validity, internal consistency and test–retest reliability suggests that it is a reliable and accurate instrument for assessing the relationship between pain and functional impairements and movement. In addition, the identification of 4 subscales provides a more detailed and accurate assessment tool for health professionals involved in the care of patients with chronic musculoskeletal pain. We consider the BioPMovQ to be an instrument that can be used in future clinical research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Centro Superior de Estudios Universitarios La Salle. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

RT: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. AP-A: Writing – review & editing. JP-M: Formal analysis, Investigation, Methodology, Writing – review & editing. DM-M:

Investigation, Writing – review & editing. FM-R: Writing – review & editing. IR-D: Writing – review & editing. MS: Formal analysis, Writing – review & editing. MG-A: Investigation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This publication has been possible thanks to a research grant received from the Colegio Professional de Fisioterapeutas de la Comunidad de Madrid, Spain (Grant No. II PI2021/04).

Acknowledgments

The author would like to express appreciation to everyone who had contributed to the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CC-L declared a shared affiliation with the author AP-A to the handling editor at the time of review.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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References

1. La Touche R. Introduciendo la dimensión motora dentro de la conceptualización de la experiencia del dolor. *J MOVE Therapeutic Sci*. (2021) 3:269–77. doi: 10.37382/JOMTS.V3I1.474

2. Simmonds MJ, Moseley GL, Vlaeyen JWS. Pain, mind, and movement: an expanded, updated, and integrated conceptualization. *Clin J Pain*. (2008) 24:279–80. doi: 10.1097/AJP.0b013e31815b607e

3. Campbell P, Bishop A, Dunn KM, Main CJ, Thomas E, Foster NE. Conceptual overlap of psychological constructs in low back pain. *Pain*. (2013) 154:1783–91. doi: 10.1016/j.pain.2013.05.035

4. Maihöfner C, Baron R, DeCol R, Binder A, Birklein F, Deuschl G, et al. The motor system shows adaptive changes in complex regional pain syndrome. *Brain*. (2007) 130:2671–87. doi: 10.1093/brain/awm131

5. Vallence A-M, Smith A, Tabor A, Rolan PE, Ridding MC. Chronic tension-type headache is associated with impaired motor learning. *Cephalalgia*. (2013) 33:1048–54. doi: 10.1177/0333102413483932

6. Holmes S, Kim A, Borsook D. The brain and behavioral correlates of motor-related analgesia (MRA). *Neurobiol Dis*. (2021) 148:105158. doi: 10.1016/J.NBD.2020.105158

7. Côté JN, Raymond D, Mathieu PA, Feldman AG, Levin MF. Differences in multi-joint kinematic patterns of repetitive hammering in healthy, fatigued and shoulder-injured individuals. *Clin Biomech*. (2005) 20:581–90. doi: 10.1016/j.clinbiomech.2005.02.012

8. Hamill J, van Emmerik RE, Heiderscheit BC, Li L. A dynamical systems approach to lower extremity running injuries. *Clin Biomech*. (1999) 14:297–308. doi: 10.1016/S0268-0033(98)90092-4

9. Lamoth CJC, Meijer OG, Daffertshofer A, Wuisman PIJM, Beek PJ. Effects of chronic low back pain on trunk coordination and back muscle activity during walking: changes in motor control. *Eur Spine J*. (2006) 15:23–40. doi: 10.1007/s00586-004-0825-y

10. Merkle S, Sluka K, Frey-Law L. The interaction between pain and movement. *J Hand Ther*. (2020) 33:60–6. doi: 10.1016/J.JHT.2018.05.001

11. Graven-Nielsen T, Svenss P, Svensson P, Arendt-Nielsen L. Effect of muscle pain on motor control: a human experimental approach. *Adv Physiother*. (2009) 2:26–38. doi: 10.1080/140381900443418

12. George SZ, Calley D, Valencia C, Beneciuk JM. Clinical investigation of pain-related fear and pain catastrophizing for patients with low Back pain. *Clin J Pain*. (2011) 27:108–15. doi: 10.1097/AJP.0b013e3181f21414

13. La Touche R, Grande-Alonso M, Arnés-Prieto P, Paris-Alemany A. How does self-efficacy influence pain perception, postural stability and range of motion in individuals with chronic low back pain? *Pain Phys*. (2019) 22:E1–E13. doi: 10.36076/ppj/2019.22.E1

14. Lambin D, Thibault P, Simmonds M, Lariviere C, Sullivan M. Repetition-induced activity-related summation of pain in patients with fibromyalgia. *Pain*. (2011) 152:1424–30. doi: 10.1016/J.PAIN.2011.02.030

15. Picavet H, Vlaeyen J, Schouten J. Pain catastrophizing and kinesiophobia: predictors of chronic low back pain. *Am J Epidemiol*. (2002) 156:1028–34. doi: 10.1093/AJE/KWF136

16. Sullivan MJL, Thibault P, Andrikonyte J, Butler H, Catchlove R, Larivière C. Psychological influences on repetition-induced summation of activity-related pain in patients with chronic low back pain. *Pain*. (2009) 141:70–8. doi: 10.1016/J.PAIN.2008.10.017

17. Bank P, Peper C, Marinus J, Beek P, van Hilten J. Motor consequences of experimentally induced limb pain: a systematic review. *Eur J Pain*. (2013) 17:145–57. doi: 10.1002/J.1532-2149.2012.00186.X

18. Hodges PW, Tucker K. Moving differently in pain: a new theory to explain the adaptation to pain. *Pain*. (2011) 152:S90–8. doi: 10.1016/j.pain.2010.10.020

19. Paris T, Misra G, Archer D, Coombes S. Effects of a force production task and a working memory task on pain perception. *J Pain*. (2013) 14:1492–501. doi: 10.1016/J.JPAIN.2013.07.012

20. Hodges P, Smeets S. Interaction between pain, movement, and physical activity: short-term benefits, long-term consequences, and targets for treatment. *Clin J Pain*. (2015) 31:97–107. doi: 10.1097/AJP.0000000000000098

21. Sullivan MJL. Toward a biopsychomotor conceptualization of pain: implications for research and intervention. *Clin J Pain*. (2008) 24:281–90. doi: 10.1097/AJP.0b013e318164bb15

22. Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med*. (2007) 30:77–94. doi: 10.1007/s10865-006-9085-0

23. Verbunt JA, Sieben JM, Seelen HAM, Vlaeyen JWS, Bousema EJ, van der Heijden GJ, et al. Decline in physical activity, disability and pain-related fear in sub-acute low back pain. *Eur J Pain*. (2005) 9:417–25. doi: 10.1016/j.ejpain.2004.09.011

24. Geisser ME, Haig AJ, Wallbom AS, Wiggert EA. Pain-related fear, lumbar flexion, and dynamic EMG among persons with chronic musculoskeletal low back pain. *Clin J Pain*. (2004) 20:61–9. doi: 10.1097/00002508-200403000-00001

25. Sarig Bahat H, Weiss PLT, Sprecher E, Krasovsky A, Laufer Y. Do neck kinematics correlate with pain intensity, neck disability or with fear of motion? *Man Ther*. (2014) 19:252–8. doi: 10.1016/j.math.2013.10.006

26. George SZ, Fritz JM, McNeil DW. Fear-avoidance beliefs as measured by the fear-avoidance beliefs questionnaire: change in fear-avoidance beliefs questionnaire is predictive of change in self-report of disability and pain intensity for patients with acute low back pain. *Clin J Pain*. (2006) 22:197–203. doi: 10.1097/01.ajp.0000148627.92498.54

27. Thomas JS, France CR. Pain-related fear is associated with avoidance of spinal motion during recovery from low back pain. *Spine*. (2007) 32:E460–6. doi: 10.1097/BRS.0b013e3180bc1f7b

28. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain*. (2000) 85:317–32. doi: 10.1016/S0304-3959(99)00242-0

29. Asghari A, Nicholas MK. Pain self-efficacy beliefs and pain behaviour. A prospective study. *Pain*. (2001) 94:85–100. doi: 10.1016/S0304-3959(01)00344-X

30. Sardá J, Nicholas MK, Asghari A, Pimenta CAM. The contribution of self-efficacy and depression to disability and work status in chronic pain patients: a comparison

between Australian and Brazilian samples. *Eur J Pain*. (2009) 13:189–95. doi: 10.1016/j.ejpain.2008.03.008

31. Sullivan MJL, Rodgers WM, Wilson PM, Bell GJ, Murray TC, Fraser SN. An experimental investigation of the relation between catastrophizing and activity intolerance. *Pain*. (2002) 100:47–53. doi: 10.1016/S0304-3959(02)00206-3

32. Hasenbring MI, Lundberg M, Parker R, Söderlund A, Bolton B, Smeets RJEM, et al. Pain, mind, and movement in musculoskeletal pain: is physical activity always health-promoting or are there detrimental aspects? *Clin J Pain*. (2015) 31:95–6. doi: 10.1097/AJP.0000000000000101

33. Feuerstein M, Beattie P. Biobehavioral factors affecting pain and disability in low back pain: mechanisms and assessment. *Phys Ther*. (1995) 75:267–80. doi: 10.1093/ptj/75.4.267

34. Artino AR, La Rochelle JS, Dezee KJ, Gehlbach H. Developing questionnaires for educational research: AMEE guide no. 87. *Med Teach*. (2014) 36:463–74. doi: 10.3109/0142159X.2014.889814

35. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*. (2010) 19:539–49. doi: 10.1007/S11136-010-9606-8

36. Andrade Ortega JA, Delgado Martinez AD, Almecija Ruiz R. Validation of the Spanish version of the neck disability index. *Spine*. (2010) 35:E114–8. doi: 10.1097/BRS.0b013e3181afea5d

37. Childs JD, Piva SR. Psychometric properties of the functional rating index in patients with low back pain. *Eur Spine J*. (2005) 14:1008–12. doi: 10.1007/s00586-005-0900-z

38. Esteve R, Ramírez-Maestre C, Peters ML, Serrano-Ibáñez ER, Ruíz-Párraga GT, López-Martínez AE. Development and initial validation of the activity patterns scale in patients with chronic pain. *J Pain*. (2016) 17:451–61. doi: 10.1016/J.JPAIN.2015.12.009

39. Fearon AM, Ganderton C, Scarvell JM, Smith PN, Neeman T, Nash C, et al. Development and validation of a VISA tendinopathy questionnaire for greater trochanteric pain syndrome, the VISA-G. *Man Ther*. (2015) 20:805–13. doi: 10.1016/J.MATH.2015.03.009

40. Ferrer-Peña R, Gil-Martínez A, Pardo-Montero J, Jiménez-Penick V, Gallego-Izquierdo T, La Touche R. Adaptation and validation of the Spanish version of the graded chronic pain scale. *Reumatol Clin*. (2016) 12:130–8. doi: 10.1016/J.REUMA.2015.07.004

41. Gloth FM, Scheve AA, Stober CV, Chow S, Prosser J. The functional pain scale: reliability, validity, and responsiveness in an elderly population. *J Am Med Dir Assoc*. (2001) 2:110–4. doi: 10.1016/S1525-8610(04)70176-0

42. Gomez-Perez L, Lopez-Martinez AE, Ruiz-Parraga GT. Psychometric properties of the Spanish version of the Tampa scale for Kinesiophobia (TSK). *J Pain*. (2011) 12:425–35. doi: 10.1016/j.jpain.2010.08.004

43. Hammond A, Prior Y, Tyson S. Linguistic validation, validity and reliability of the British English versions of the disabilities of the arm, shoulder and hand (DASH) questionnaire and QuickDASH in people with rheumatoid arthritis. *BMC Musculoskelet Disord*. (2018) 19:118. doi: 10.1186/S12891-018-2032-8

44. Kovacs FM, Llobera J, Gil Del Real MT, Abraira V, Gestoso M, Fernández C, et al. Validation of the Spanish version of the Roland-Morris questionnaire. *Spine*. (2002) 27:538–42. doi: 10.1097/00007632-200203010-00016

45. Kovacs FM, Muriel A, Medina JM, Abraira V, Sánchez MDC, Jaúregui JO. Psychometric characteristics of the Spanish version of the FAB questionnaire. *Spine*. (2006) 31:104–10. doi: 10.1097/01.brs.0000193912.36742.4f

46. Langenfeld A, Bastiaenen C, Sieben J, Swanenburg J. Development and validation of a self-administered neck mobility assessment tool (S-ROM-neck) in chronic neck pain patients. *Musculoskelet Sci Pract*. (2018) 37:75–9. doi: 10.1016/J.MSKSP.2018.04.004

47. Lauche R, Cramer H, Langhorst J, Michalsen A, Dobos GJ. Reliability and validity of the pain on movement questionnaire (POM) in chronic neck pain. *Pain Med*. (2014) 15:1850–6. doi: 10.1111/pme.12534

48. Martín-Aragón M, Pastor MA, Rodríguez-MaríN J, March MJ, Lledó A, López-Roig . Percepción de autoeficacia en dolor crónico: adaptación y validación de la Chronic Pain Self-Efficacy Scale. *Rev de Psicol de La Salud*. (1999) 11:53–75.

49. Naghdi S, Nakhostin Ansari N, Yazdanpanah M, Feise RJ, Fakhari Z. The validity and reliability of the functional rating index for evaluating low back pain in athletes. *Scand J Med Sci Sports*. (2015) 25:840–5. doi: 10.1111/sms.12447

50. Neblett R, Mayer TG, Hartzell MM, Williams MJ, Gatchel RJ. The fear-avoidance components scale (FACS): development and psychometric evaluation of a new measure of pain-related fear avoidance. *Pain Pract*. (2016) 16:435–50. doi: 10.1111/PAPR.12333

51. Payares K, Lugo LH, Morales V, Londoño A. Validation in Colombia of the Oswestry disability questionnaire in patients with low back pain. *Spine*. (2011) 36:E1730–5. doi: 10.1097/BRS.0b013e318219d184

52. Wolff SV, Willburger R, Hallner D, Rusu AC, Rusche H, Schulte T, et al. Avoidance-endurance fast screening (AE-FS): Content and predictive validity of a 9-item screening instrument for patients with unspecific subacute low back pain. *Schmerz*. (2018) 32:283–92. doi: 10.1007/S00482-018-0310-X

53. Smith JA. Beyond the divide between cognition and discourse: using interpretative phenomenological analysis in health psychology. *Psychol Health*. (1996) 11:261–71. doi: 10.1080/08870449608400256

54. Duque H, Aristizábal Díaz-Granados ET. Análisis fenomenológico interpretativo. *Pensando Psicología*. (2019) 15:1–24. doi: 10.16925/2382-3984.2019.01.03

55. Pringle J, Drummond J, McLafferty E, Hendry C. Interpretative phenomenological analysis: a discussion and critique. *Nurse Res*. (2011) 18:20–4. doi: 10.7748/nr2011.04.18.3.20.c8459

56. Tuffour I. A critical overview of interpretative phenomenological analysis: a contemporary qualitative research approach. *J Healthc Commun*. (2017) 2:52. doi: 10.4172/2472-1654.100093

57. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. (1995) 311:376–80. doi: 10.1136/bmj.311.7001.376

58. Aiken LR. Three coefficients for analyzing the reliability and validity of ratings. *Educ Psychol Meas*. (1985) 45:131–42. doi: 10.1177/0013164485451012

59. Farnik M, Pierzchała WA. Instrument development and evaluation for patient-related outcomes assessments. *Patient Relat Outcome Meas*. (2012) 3:1–7. doi: 10.2147/PROM.S14405

60. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. *Pain*. (2015) 156:1003–7. doi: 10.1097/J.PAIN.0000000000000160

61. Perrot S, Cohen M, Barke A, Korwisi B, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: chronic secondary musculoskeletal pain. *Pain*. (2019) 160:77–82. doi: 10.1097/J.PAIN.0000000000001389

62. Lloret-Segura S, Ferreres-Traver A, Hernández-Baeza A, Tomás-Marco I. El Análisis Factorial Exploratorio de los Ítems: una guía práctica, revisada y actualizada. *Anales Psicol*. (2014) 30:1151–69. doi: 10.6018/ANALESPS.30.3.199361

63. Ferrando Piera PJ, Anguiano Carrasco C. El análisis factorial como técnica de investigación en psicología. *Papeles Del Psicólogo*. (2010) 31:18–33. Available at: https://www.redalyc.org/articulo.oa?id=77812441003

64. Walter SD, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. *Stat Med*. (1998) 17:101–10. doi: 10.1002/(SICI)1097-0258(19980115)17:1<101::AID-SIM727>3.0.CO;2-E

65. Arifin WN. A web-based sample size calculator for reliability studies. *Educ Med J*. (2018) 10:67–76. doi: 10.21315/EIMJ2018.10.3.8

66. Jöreskog KG, Goldberger AS. Factor analysis by generalized least squares. *Psychometrika*. (1972) 37:243–60. doi: 10.1007/BF02306782/METRICS

67. Izquierdo I, Olea J, Abad FJ. Exploratory factor analysis in validation studies: uses and recommendations. *Psicothema*. (2014) 26:395–400. doi: 10.7334/PSICOTHEMA2013.349

68. Kaiser HF. An index of factorial simplicity. *Psychometrika*. (1974) 39:31–6. doi: 10.1007/BF02291575

69. Ferguson E, Cox T. Exploratory factor analysis: a user' s guide. *Int J Select Assess*. (1993) 1:84–94. doi: 10.1111/j.1468-2389.1993.tb00092.x

70. Garrido LE, Abad FJ, Ponsoda V. Are fit indices really fit to estimate the number of factors with categorical variables? Some cautionary findings via Monte Carlo simulation. *Psychol Methods*. (2016) 21:93–111. doi: 10.1037/MET0000064

71. Golino H, Shi D, Christensen AP, Garrido LE, Nieto MD, Sadana R, et al. Investigating the performance of exploratory graph analysis and traditional techniques to identify the number of latent factors: a simulation and tutorial. *Psychol Methods*. (2020) 25:292–320. doi: 10.1037/MET0000255

72. Golino H., Christensen A. P. (2022). *EGAnet: exploratory graph analysis – a framework for estimating the number of dimensions in multivariate data using network psychometrics. R Package Version 2.0.2*. Available at: https://r-ega.net

73. Revelle W. *psych: procedures for psychological, psychometric, and personality research*. Evanston, Illinois: Northwestern University (2023) R Package Version 2.3.3.

74. Costello AB, Osborne J. Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis. *Pract Assess Res Eval*. (2005) 10:7. doi: 10.7275/jyj1-4868

75. Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol*. (2007) 60:34–42. doi: 10.1016/j.jclinepi.2006.03.012

76. Sendlbeck M, Araujo EG, Schett G, Englbrecht M. Psychometric properties of three single-item pain scales in patients with rheumatoid arthritis seen during routine clinical care: a comparative perspective on construct validity, reproducibility and internal responsiveness. *RMD Open*. (2015) 1:e000140. doi: 10.1136/rmdopen-2015-000140

77. García Campayo J, Rodero B, Alda M, Sobradiel N, Montero J, Moreno S. Validación de la versión española de la escala de la catastrofización ante el dolor (Pain Catastrophizing Scale) en la fibromialgia. *Med Clin*. (2008) 131:487–92. doi: 10.1157/13127277

78. Martín-Aragón M, Pastor M, Rodríguez-Marín J, March M, Lledó A, López-Roig S, et al. Percepción de autoeficacia en dolor crónico. Adaptación y validación de la chronic pain self-efficacy scale. *Revista de Psicología Salud*. (1999) 11:53–75.

79. Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrika*. (1951) 16:297–334. doi: 10.1007/BF02310555

80. Trizano-Hermosilla I, Alvarado JM. Best alternatives to Cronbach's alpha reliability in realistic conditions: congeneric and asymmetrical measurements. *Front Psychol*. (2016) 7:769. doi: 10.3389/FPSYG.2016.00769

81. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. (2016) 15:155–63. doi: 10.1016/J.JCM.2016.02.012

82. Haley SM, Fragala-Pinkham MA. Interpreting change scores of tests and measures used in physical therapy. *Phys Ther*. (2006) 86:735–43. doi: 10.1093/ptj/86.5.735

83. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Condit Res*. (2005) 19:231. doi: 10.1519/15184.1

84. Šimundić A-M. Measures of diagnostic accuracy: basic definitions. *EJIFCC*. (2008) 19:203–11.

85. Böhning D, Böhning W, Holling H. Revisiting Youden's index as a useful measure of the misclassification error in meta-analysis of diagnostic studies. *Stat Methods Med Res*. (2008) 17:543–54. doi: 10.1177/0962280207081867

86. López-Ratón M, Rodríguez-Álvarez MX, Cadarso-Suárez C, Gude-Sampedro F. OptimalCutpoints: an R package for selecting optimal cutpoints in diagnostic tests. *J Stat Softw*. (2014) 61:1–36. doi: 10.18637/JSS.V061.I08

87. Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res*. (2013) 22:1889–905. doi: 10.1007/s11136-012-0344-y

88. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, et al. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 2—assessing respondent understanding. *Value Health*. (2011) 14:978–88. doi: 10.1016/j.jval.2011.06.013

89. Beavers AS, Lounsbury JW, Richards JK, Huck SW, Skolits GJ, Esquivel SL. Practical considerations for using exploratory factor analysis in educational research. *Pract Assess Res Eval*. (2013) 18:6. doi: 10.7275/qv2q-rk76

90. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychol Bull*. (2007) 133:581–624. doi: 10.1037/0033-2909.133.4.581

91. Streiner DL, Norman GR. *Health measurement scales: a practical guide to their development and use. In health measurement scales: a practical guide to their development and use (3rd)*. New York: Oxford University Press (2008).

92. de Vet HC, Terwee CB, Ostelo RW, Beckerman H, Knol DL, Bouter LM. Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes*. (2006) 4:54. doi: 10.1186/1477-7525-4-54

93. Rolstad S, Adler J, Rydén A. Response burden and questionnaire length: is shorter better? A review and meta-analysis. *Value Health*. (2011) 14:1101–8. doi: 10.1016/j.jval.2011.06.003

94. Vickers AJ. Multiple assessment in quality of life trials: how many questionnaires? How often should they be given? *J Soc Integr Oncol*. (2006) 4:135–8. doi: 10.2310/7200.2006.017

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 06 June 2024
DOI 10.3389/fmed.2024.1381515

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OPEN ACCESS

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RECEIVED 03 February 2024
ACCEPTED 23 May 2024
PUBLISHED 06 June 2024

CITATION
Doménech-García V, Pecos-Martín D, Blasco-Abadía J, Bellosta-López P and López-Royo MP (2024) Placebo and nocebo effects of percutaneous needle electrolysis and dry-needling: an intra and inter-treatment sessions analysis of a three-arm randomized double-blinded controlled trial in patients with patellar tendinopathy.
Front. Med. 11:1381515.
doi: 10.3389/fmed.2024.1381515

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Placebo and nocebo effects of percutaneous needle electrolysis and dry-needling: an intra and inter-treatment sessions analysis of a three-arm randomized double-blinded controlled trial in patients with patellar tendinopathy

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Objective: This study aimed to investigate the influence of potential placebo and nocebo effects on pain perception of percutaneous needle electrolysis (PNE) in individuals with patellar tendinopathy.

Methods: In this secondary analysis of a three-arm randomized double-blinded controlled trial, intra and inter-session pain perception data from 48 sporting participants with patellar tendinopathy between 18 and 45 years were investigated. Participants were divided into 3 parallel groups: "no-sham group" [PNE intervention], "single-sham group" [sham PNE by using dry needling], and "double-sham group" [sham PNE by using sham needles]. Every group received 4 sessions of the needling therapies targeting the patellar tendon over 8 weeks and was instructed to perform a unilateral eccentric exercise program of the quadriceps muscle on the affected side. Clinical and needle-related pain was assessed before, during, and after each treatment session using a visual analog scale.

Results: No differences were found between groups intra- or inter-session in terms of pain reduction ($P = 0.424$) despite clinical pain decreased in all groups since the first treatment session ($P < 0.001$). Furthermore, although the double-sham group showed a lower percentage of participants reporting needle-related pain during needle intervention ($P = 0.005$), the needle-related pain intensity after needle intervention was similar between groups ($P = 0.682$). Moreover, there were no group differences for the duration of pain sensation after any needle intervention ($P = 0.184$), extending in many cases beyond 24 h.

Conclusion: Needling therapies for individuals with patellar tendinopathy are prone to elicit placebo effects regarding clinical pain and nocebo effects

regarding needling-related pain. Clinicians and physical therapists treating musculoskeletal pain conditions should consider the added value and potential mechanisms of action before routinely using needle techniques.

KEYWORDS

placebo, nocebo, needling techniques, percutaneous needle electrolysis, dry needling, tendinopathy

1 Introduction

Musculoskeletal painful disorders represent the primary contributor to rehabilitation needs and a major worldwide health problem (1). Patients with musculoskeletal painful disorders often seek a physiotherapist for assistance, and physiotherapists employ various therapeutic interventions, which are often complex, to reduce pain and disability (2). Ideally, specific treatment effects drive most of these changes, although non-specific effects such as regression to the mean, natural history, and contextual effects also contribute (3). Placebo effects can be described as beneficial effects that are not due to an active treatment components (4). and depends on contextual factors related to the reduction of symptoms caused by the psychosocial context, such as positive expectations or patient satisfaction, and not solely by the properties of the treatment itself (5). In contrast, nocebo effects are adverse treatment outcomes elicited by non-active treatment components (4) and are produced by negative expectations or context that may exacerbate the patient's symptoms (6).

Clinically, placebo and nocebo effects are important during therapy administration, representing the result of the adjuvant or harmful use of contextual factors (7, 8). Information provided about treatment, patient expectations, previous encounters with a procedure, therapist characteristics, and the therapeutic relationship between the patient and the therapist can all generate these effects (8–13). While isolated placebo treatments seem to lack clinical meaningfulness, recent meta-analysis findings show that within the realm of non-pharmacological conservative interventions for musculoskeletal conditions, the placebo effect can contribute up to 30% of the minimally clinically important difference (14). Interestingly, the authors hypothesized that certain interventions such as needles or manual therapy may elicit even more substantial placebo effects. However, despite adequately-designed randomized controlled clinical trials that should include placebo controls to disentangle placebo and nocebo effects from the general effect of the intervention (15), only a very small proportion of randomized controlled clinical trials testing physiotherapy interventions do so (16).

In recent years, minimally invasive procedures for managing musculoskeletal painful disorders, such as dry needling (DN) or percutaneous needle electrolysis (PNE), have gained global popularity (17, 18). PNE is an invasive approach that involves applying a galvanic current through an acupuncture needle into the soft tissue lesion to elicit a local inflammatory response (19). Discomfort related to applying galvanic current could make PNE an unpleasant procedure for the patient. Indeed, the most common adverse effects of PNE, such as pain during the intervention and in the days following treatment, (18) are similar to those observed in DN (20). Furthermore, using needles as a therapeutic tool may cause a certain degree of apprehension in the patient, (20) and fear of needles or fear of pain could predispose the subject to react with negative emotions to pain and in anticipation of pain (21, 22). Conversely, it is unknown to what extent these interventions produce improvements in patients with musculoskeletal painful disorders due to non-specific effects such as placebo hypoalgesia. Placebo hypoalgesia is observed when a sham intervention results in pain relief and can also be acquired through operant conditioning. This uncertainty is probably due to the challenge that represents its evaluation represents, not only in needling interventions but in musculoskeletal interventions in general (15). Although the PNE technique has been compared with placebo interventions, the potential influence of the placebo effect on the results has not been considered (23).

Therefore, this study aimed to investigate the influence of potential placebo and nocebo effects on pain perception of an intratissue PNE-based intervention in individuals with patellar tendinopathy.

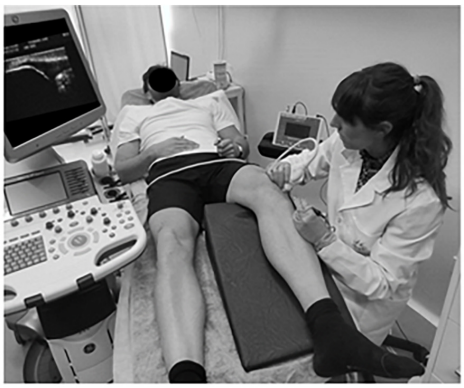
2 Material and methods

2.1 Study design and settings

This study was part of a three-arm randomized double-blinded controlled trial (ClinicalTrial.gov: NCT02498795) (24). The study followed the Helsinki Declaration and was approved by the local Ethics Committee (C.P.−C.I. PI15/0017), and all participants consented their enrolling in this study.

2.2 Participants

Adults aged between 18 and 45 years were recruited from various sports clubs and federations. To be eligible, participants had to meet specific inclusion criteria: (1) experienced anterior knee pain below the patella while engaging in sports for over 3 months; (2) engaged in sports activities at least 3 times a week; and (3) scored below 80 on the Victorian Institute of Sport Assessment-Patellar questionnaire (VISA-p). Exclusion criteria included: (1) knee surgery in the past 6 months; (2) patellar tendon corticosteroid injection in the past 3 months; (3) diagnosed with chronic joint disease; (4) contraindications for needling (e.g., needle phobia, needle material allergy); (5) consumption



Controlled factors	Groups		
	No-sham	Single-sham	Double-sham
Same language & command	✓	✓	✓
Same non-verbal communication	✓	✓	✓
Same setting & therapist outfit	✓	✓	✓
Same ritual from welcome to farewell	✓	✓	✓
Participant blinded to the ultrasound image	✓	✓	✓
Galvanic current	✓	X	X
Needle penetration	✓	✓	X

FIGURE 1
Illustration depicting the common setting and intervention procedures for all three groups, along with a list of controlled factors.

of anti-inflammatory, analgesic, or antibiotic medications within the past 48 h; and (6) undergoing concurrent physiotherapy treatment. Additionally, ultrasound examination of the knee joint and adjacent musculoskeletal structures was conducted before enrollment in the study. This examination aimed to exclude the presence of joint effusion or signs of inflammation and to identify the presence of degenerative signs, characterized by a hypoechoic area in the body of the tendon. None of the participants in the final selected sample had received prior needling treatment in the tendon.

2.3 Groups and interventions

Participants were divided into three groups according to the intervention received: (1) PNE [no-sham group], (2) sham PNE by using DN [single-sham group], and (3) sham PNE by using sham needles [double-sham group]. The setting and procedure followed with each participant was similar regardless of group, isolating the effects related to galvanic current and needling (**Figure 1**). All interventions were targeted at the patellar tendon.

2.3.1 No-sham group

For the no-sham group, 0.25 × 0.25 mm needles (*APS safety tube dry needles; Agupunt*) were connected to the electrolysis device (*model EPI®, CESMAR Electromedicina. S.L., Spain*). The researcher utilized ultrasonography to guide the procedure, ensuring precise application to the injured area and maintaining safety. The needle was inserted into the injured area three times, targeting the hypoechoic region within the patellar tendon. Each insertion lasted 3 s and involved the use of 3 mA of galvanic current.

2.3.2 Single-sham group

In the single-sham group, the needle was inserted following the same protocol as in the no-sham group. The only difference was that the electrolysis device was turned on with a current intensity of 0 mA (i.e., no galvanic current). The needle reached the relevant treatment area in the patellar tendon guided by ultrasonography.

2.3.3 Double-sham group

For the double-sham group, a sham needle was placed upon the treatment zone, simulating the same procedure as in the other groups. In addition, the needle was manipulated in and out to simulate a real treatment. The holder had a cover over the bottom part to prevent the needle from contacting the skin.

2.4 Procedure

Participants underwent 4 intervention sessions over an 8-week period, with each session spaced 2 weeks apart. During each session, a standardized procedure was followed to ensure participant blinding during needle interventions, attempting to overcome biases found in previous studies on needling techniques (25). Participants were positioned supine with their knee flexed at 20°, supported by a pillow. The researcher performing the intervention wore latex gloves and cleansed the area with a 70% propan-2-ol antiseptic solution. A disposable protective cover was applied to a lubricated ultrasound probe (*Logic S7 Expert, General Electric Healthcare*), which was used for real-time ultrasound guidance. The ultrasound display screen was positioned behind the participants. Each participant held the anode connected to the electrolysis device and received the following instruction: "During the needle intervention, please try to remain still. The treatment may cause some pain or discomfort. If you experience any, please let me know, and I will stop immediately." After needle removal, the area was gently compressed with cotton wool for 5 s (**Figure 1**).

At the end of the study, participants were asked via email to guess the type of treatment they received. The options provided were: "No needling treatment," "Needling treatment," or "I don't know." If participants selected "Needling treatment," they were further asked to specify whether they received PNE or DN, with the options being "PNE," "DN," or "I don't know."

Complementary to the real or sham needle intervention, all participants were instructed to perform a unilateral eccentric exercise program of the quadriceps muscle on the affected side, specifically aimed at the patellar tendon. This program consisted of performing 3 sets of 15 repetitions daily on a decline board (26). The correct execution of the exercise as well as the follow-up of the prescribed program was monitored by the research team every two weeks, coinciding with the day the participant received the intervention.

2.5 Randomization

Participants who fulfilled the inclusion criteria and consented to participate in the trial were randomly assigned by a researcher

TABLE 1 Detailed description of the outcome variables included in the study.

Variable name	Variable description
Clinical pain intensity before needle intervention.	Participants rated their pain before each needle intervention using a Visual Analogue Scale where a score of 0 indicated "absence of pain", whereas a score of 10 represented the "maximum tolerable pain".
Needle-related pain during needle intervention.	Participants were asked to report by "yes" or "no" if they had pain during the needle intervention (i.e., Have you felt any pain during the procedure?).
Needle-related pain intensity after needle intervention.	Participants rated their level of pain in the tendon area after each needle intervention (i.e., How painful is the area of the puncture after the procedure?) by using a Visual Analogue Scale where a score of 0 indicated "absence of pain", whereas a score of 10 represented the "maximum tolerable pain".
Clinical pain intensity during a provocative test after needle intervention.	Five minutes after the real or sham needle intervention, participants performed a provocative test for the patellar tendon, consisting of a half single squat (until 90 degrees of knee flexion) performed with the symptomatic leg. Upon completion, participants were asked to rate their pain intensity during the provocative test using a Visual Analogue Scale where a score of 0 indicated "absence of pain" whereas a score of 10 represented the "maximum tolerable pain".
Clinical pain reduction after needle intervention.	Pain reduction after needle intervention was calculated by subtracting pain intensity values before needle intervention from pain intensity values during the provocative test.
Days until needle-related pain sensation completely disappears after needle intervention.	At the beginning of each intervention session, except for the first session, the participants reported the duration of pain sensation after the last intervention (i.e., How long was the area of the puncture painful after the last session?), where the possible answers were: "No pain or soreness", " < 24 h", "24–48 h", or " > 48 h".

not involved in the study by generating random participant sequences with a 1:1:1 allocation using an opaque envelope, with a block size of 15 participants, using a computer program (Randomizer).[1]

2.6 Outcome measures

Assessments were made by an assessor blinded to group allocation. The primary outcomes for placebo and nocebo effects were clinical pain reduction after needle intervention and needle-related pain intensity after needle intervention, respectively. While the secondary outcomes were clinical pain intensity before needle intervention, clinical pain intensity during a provocative test after needle intervention, needle-related pain during needle intervention, and days until needle-related pain sensation completely disappears after needle intervention. Outcome measures in this study are detailed in Table 1. Description and clinical findings in VISA-p and ultrasonographic measures after the 8-week period are available elsewhere (27).

1 https://www.randomizer.org

2.7 Statistical analysis

Statistical analysis was performed using SPSS, v.25 (IBM Corp., Chicago, IL). A P-value < 0.05 was accepted as a significant difference between compared variables. Variables distribution was assessed using the Shapiro-Wilk test and described in percentage, mean and standard deviation or median and interquartile range, according to the distribution of data. Differences between groups were compared using chi-squared tests (χ^2) for categorical data and mixed-model repeated-measures analysis of variance (RM-ANOVA) for continuous data with *time* (session 1, 2, 3, and 4) as within and *group* (no-sham group, single-sham group, and double-sham group) as between factors. Pairwise Bonferroni comparisons were performed as post hoc analyses.

2.8 Sample size calculation

The original sample size was calculated based on the VISA-p, and details were reported elsewhere (27). However, a secondary post hoc sample size calculation with G*Power (v3.1.9.2, Heinrich-Heine-University, Dusseldorf, Germany) revealed the feasible sample size for a mixed model RM-ANOVA with three groups (no-sham group, single-sham group, and double-sham group) participating in four experimental sessions. With a power of 90% and an alpha level of 0.01, a total of 42 participants (14 per group) were needed for participation to detect the minimal important difference of 1.2 points (partial $\eta^2 = 0.05$) in the Visual Analogue Scale (28).

3 Results

Recruitment began in January 2019 and was completed in December 2019. Out of the 72 subjects assessed for eligibility, 5 declined to participate, while 19 did not meet eligibility criteria (24). A total of 48 participants (16 per group) were enrolled and received the allocated intervention. One participant in the no-sham group withdrew after the first session due to moving to another city and was subsequently removed from the statistical analysis. Figure 2 shows the study flowchart.

Table 2 shows the characteristics of the 47 participants who completed the study. No significant differences were found between the groups regarding sociodemographic and clinical variables at baseline. Participants who completed the blinding questionnaire ($n = 29$; no-sham group: 12; single-sham group: 9, and double-sham group: 8) reported receiving a needle intervention, from which 82% ($n = 23$) indicated PNE as the needle intervention.

3.1 Clinical pain intensity before needle intervention

No *time* and *group* interaction (RM-ANOVA: $F_{6,132} = 1.1$; $P = 0.357$) was found for pain intensity before needle intervention, indicating no differences in the evolution of pain intensity between groups across sessions. However, a *time* effect was found (RM-ANOVA: $F_{3,132} = 16.5$; $P < 0.001$), indicating that the three

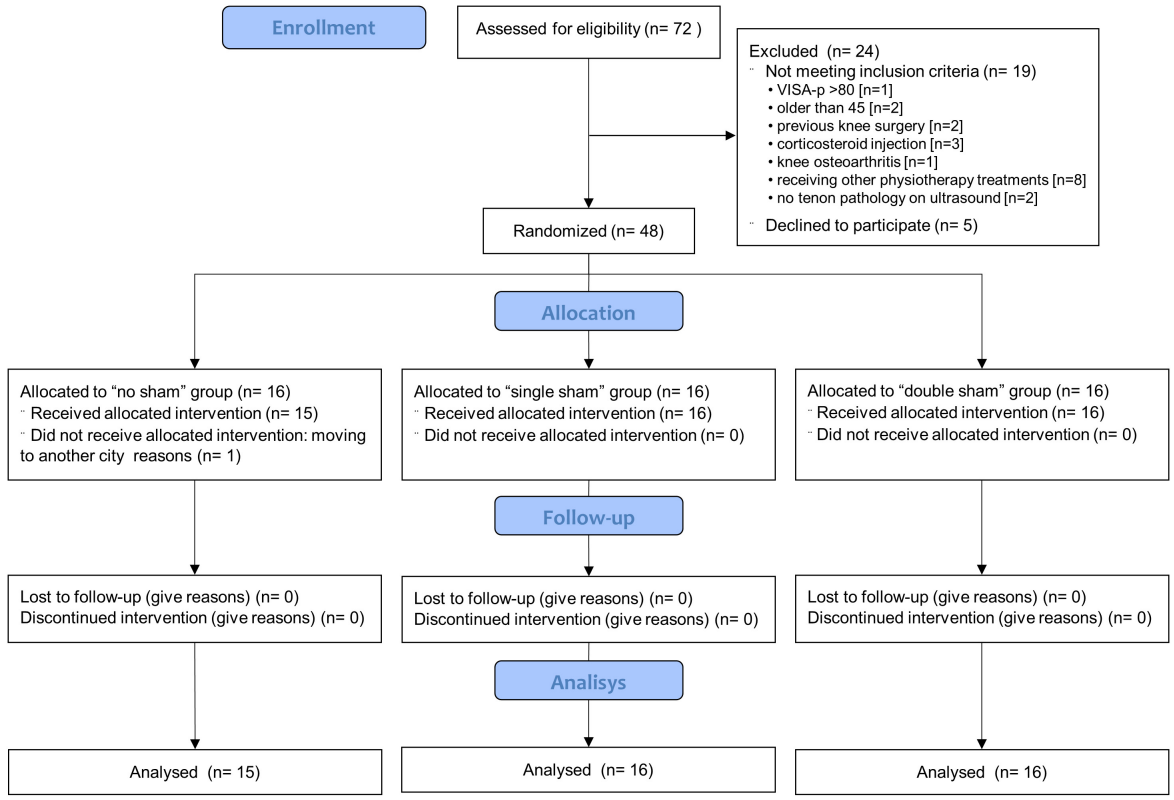


FIGURE 2
Participant flow chart. DN, dry needling group; PNE, Percutaneous needle electrolysis group.

TABLE 2 **Participant characteristics in the three study groups.**

	No sham (n = 15)	Single sham (n = 16)	Double sham (n = 16)	P value
Age, years	36.0 [28.0–39.5]	33.0 [31.0–43.5]	36.5 [31.2–39.0]	0.57
Women, n (%)	2 (13.3%)	3 (18.8%)	1 (6.3%)	0.57
Weight, kg	80.0 [66.9–89.9]	75.5 [62.5–83.3]	80.0 [73.2–84.0]	0.50
Height, cm	179 [173–181]	176 [168–185]	179 [176–182]	0.83
BMI, kg/m^2	24.4 [22.7–27.1]	23.9 [21.7–26.2]	24.9 [23.0–26.6]	0.32
Sport activity, times/week	4 [4–5]	5 [4–7]	5 [4–7]	0.19
Symptoms duration, months	15.0 [12.0–24.0]	10.5 [4.3–18.0]	10.5 [6.0–23.0]	0.98
VISA-P	48.9 [30.0–75.0]	57.2 [29.0–79.0]	55.5 [42.0–79.0]	0.16

Median [interquartile range: 25th-75th percentiles]. BMI, Body Mass Index; VISA-P, Victorian Institute of Sports Assessment Questionnaire, patellar tendon.

groups decreased pain intensity over the sessions. Post-hoc analysis showed a lower pain intensity at the beginning of session 4 compared to session one in all groups (no-sham group: $P < 0.001$; single-sham group: $P = 0.011$, and double-sham group: $P = 0.037$). See Table 3.

3.2 Needle-related pain during needle intervention

Significant differences existed between the frequencies of participants reporting pain in the three groups during all the needle interventions ($\chi^2 \geq 10.6$; $P \leq 0.005$). Specifically, 80% of the no-sham group, 81% to 100% of the single-sham group, and 25% to 44% of the double-sham group reported pain during needle intervention. See Table 3.

3.3 Needle-related pain intensity immediately after needle intervention

No *time* and *group* interaction (RM-ANOVA: $F_{6,132} = 0.7$; $P = 0.682$) or *time* effect (RM-ANOVA: $F_{3,132} = 1.7$; $P = 0.168$) was found for pain intensity after needle intervention, indicating that the painful sensation after needle intervention was similar between groups in all sessions. See Table 3.

TABLE 3 Outcome measures in the three study groups.

	No sham (n = 15)	Single sham (n = 16)	Double sham (n = 16)	P value
Clinical pain intensity before needle intervention (VAS 0–10)				0.357[§]
Session 1	5.1 ± 1.6	4.0 ± 1.8	5.0 ± 2.1	
Session 2	4.5 ± 2.2	3.0 ± 1.5	4.3 ± 2.0	
Session 3	3.6 ± 1.6	3.1 ± 2.2	4.5 ± 2.5	
Session 4	2.6 ± 1.7	2.3 ± 1.9	3.5 ± 2.1	
Needle-related pain during needle intervention (n yes, %)				
Session 1	12 (80%)*	14 (88%)*	4 (25%)	< 0.001[#]
Session 2	12 (80%)*	16 (100%)*	6 (38%)	< 0.001[#]
Session 3	12 (80%)*	15 (94%)*	7 (44%)	0.005[#]
Session 4	12 (80%)*	13 (81%)*	4 (25%)	< 0.001[#]
Needle-related pain intensity immediately after needle intervention (VAS 0–10)				0.682[§]
Session 1	1.7 ± 1.9	1.7 ± 1.9	1.1 ± 2.1	
Session 2	2.0 ± 2.5	2.1 ± 2.4	1.3 ± 2.0	
Session 3	1.9 ± 2.3	1.3 ± 2.1	1.3 ± 1.9	
Session 4	1.3 ± 2.2	1.5 ± 1.8	0.8 ± 1.6	
Clinical pain intensity during a provocative test after needle intervention (VAS 0–10)				0.937[§]
Session 1	0.0 ± 0.1	0.7 ± 1.4	0.9 ± 1.5	
Session 2	0.5 ± 1.8	0.9 ± 1.7	0.8 ± 1.6	
Session 3	0.3 ± 1.0	0.3 ± 1.0	0.5 ± 1.4	
Session 4	0.0 ± 0.0	0.3 ± 1.0	0.4 ± 1.2	
Duration of pain sensation after needle intervention (n, %)				
Session 1				0.284[#]
No pain	1 (7%)	0 (0%)	0 (0%)	
< 24 h	8 (53%)	11 (69%)	8 (50%)	
24–48 h	6 (40%)	3 (19%)	8 (50%)	
> 48 h	0 (0%)	2 (13%)	0 (0%)	
Session 2				0.948[#]
No pain	2 (13%)	2 (13%)	3 (19%)	
< 24 h	9 (60%)	8 (50%)	8 (50%)	
24–48 h	4 (27%)	6 (38%)	5 (31%)	
> 48 h	0 (0%)	0 (0%)	0 (0%)	
Session 3				0.670[#]
No pain	2 (13%)	2 (13%)	3 (19%)	
< 24 h	8 (53%)	12 (75%)	8 (50%)	
24–48 h	3 (20%)	2 (13%)	4 (25%)	
> 48 h	2 (13%)	0 (0%)	1 (6%)	

Mean ± SD. VAS, Visual Analogue Scale. [§]P value after RM-ANOVA. [#]P value after chi-squared test. *$P < 0.05$ indicating a higher frequency compared to the double sham group.

3.4 Clinical pain intensity during a provocative test after needle intervention

No *time* and *group* interaction (RM-ANOVA: $F_{6,132} = 0.4$; $P = 0.937$) or *time* effect (RM-ANOVA: $F_{3,132} = 1.7$; $P = 0.179$) was found for painful sensation after needle intervention, indicating that the painful sensation after needle intervention was similar between groups in all sessions. See Table 3.

3.5 Clinical pain reduction after needle intervention

No *time* and *group* interaction (RM-ANOVA: $F_{6,132} = 1.0$; $P = 0.424$) was found for pain reduction after needle intervention, indicating no differences in the evolution of pain reduction between groups across sessions. However, a *time* effect was found (RM-ANOVA: $F_{3,132} = 6.3$; $P < 0.001$), indicating that pain reduction

within the three groups differed between sessions. *Post hoc* analysis showed a lower pain reduction at session 2 ($P = 0.027$) and session 4 ($P = 0.001$), compared to session 1 in all groups. See **Figure 3**.

3.6 Days until needle-related pain sensation completely disappears after needle intervention

There were no differences between the frequencies of participants reporting the duration of pain sensation after any needle intervention ($\chi^2 \leq 8.8$; $P \geq 0.184$). See **Table 3**.

3.7 Adverse effects

No adverse events were reported other than the previously described needle-related pain itself and the post-puncture pain described above, which were part of the outcome measures.

4 Discussion

This study is the first to investigate placebo and nocebo effects potentially associated with an invasive needle technique by implementing single-sham and double-sham procedures in individuals with patellar painful tendinopathy. The findings suggest that needling techniques, specifically PNE, induce significant placebo and nocebo effects on both clinical and needle-related pain, respectively.

4.1 Contextual effects in clinical tendon pain

The three groups similarly improving their pain over time, both at rest (before and after intervention) and during a functional provocative test, might reflect different effects. On the one hand, these findings might only indicate a direct positive effect of eccentric exercise on tendon pain, as previously reported (29). Furthermore, it is unlikely that there was no effect at all from the PNE intervention on pain, as previous studies have found a pain reduction effect in tendinopathies (18). Therefore, it is unlikely that eccentric exercise explains the clinical pain improvements observed in the three groups.

On the other hand, the persistence of patellar tendinopathy symptoms for 18 months in the present study, consistent with previous literature, (30) suggests that non-specific effects such as regression to the mean or natural history might partially explain the observed improvements in clinical pain. However, both the present study and previous literature show a high standard deviation in the duration of symptoms, either at the mean value or above. This substantial variability makes regression to the mean and natural history less likely to account for the clinical pain improvement observed in the three groups. Moreover, it is important to note that these non-specific factors would not explain the observed nocebo effect in needle-related pain. Therefore, it can be inferred that non-specific effects, such as placebo and nocebo responses, are at least partially responsible for the reduction in pain among patients with patellar tendinopathy undergoing needling therapies.

A recent study has shown that expectations may not play as significant role as prior therapeutic experiences in placebo and nocebo responses in healthy individuals (31). Although the connection between these non-specific effects and the psychological characteristics of the participants remains unknown, a recent study with high methodological quality and one of the largest samples in placebo research has shown that individuals with chronic pain benefiting from placebo are characterized by low emotional stress, pain-related fear, and catastrophizing (5). However, catastrophizing has been linked to patellar tendinopathy only in individuals with more severe symptoms (32). The present study, based on the baseline pain VAS values of participants, indicates that in most cases, tendinopathies were moderate to low. Therefore, it can be hypothesized that the sample in the current study did not have a high psychological burden and were more likely to benefit from placebo effects.

4.2 Contextual effects in needling-related pain

As expected, most participants reported pain during the intervention when a needle was inserted into the tendon. Interestingly, up to 44% of participants in the double-sham group also reported pain during intervention. Furthermore, all groups reported the same amount of needle-related pain immediately after the intervention, and up to 25% of participants in the double-sham group continued experiencing pain even 24-48h after the intervention. Overall, these findings indicate that needling interventions are susceptible to non-specific effects, aligning with previous literature (33).

Although not measured on participants, subjective factors such as expectations may have modulated pain (34) after the needling intervention (35). Increased pain due to the expectation of more pain following an intervention is a nocebo effect observed previously (36, 37). A study in patients with chronic shoulder pain found increased mechanical hyperalgesia immediately following sham dry needling that lasted for 24h in individuals with shoulder pain. The study attributed these changes to a nocebo effect generated by negative expectations associated with the instructions given before the procedure (38). In addition to negative expectations, other factors that might have mediated a nocebo effect in post needling-related pain include classical conditioning, observational learning, (39) and prior therapeutic experiences (31).

4.3 Clinical implications

These findings clearly reflect that needling interventions in individuals with patellar tendinopathy involve intrinsic positive and negative non-specific factors. Therefore, the contextual factors of needling therapies can trigger both placebo and nocebo responses and must be considered in the clinical context. This serves as a general recommendation for physiotherapists and musculoskeletal clinicians, who are encouraged to understand and manage the contextual factors [e.g., patients' expectations, past

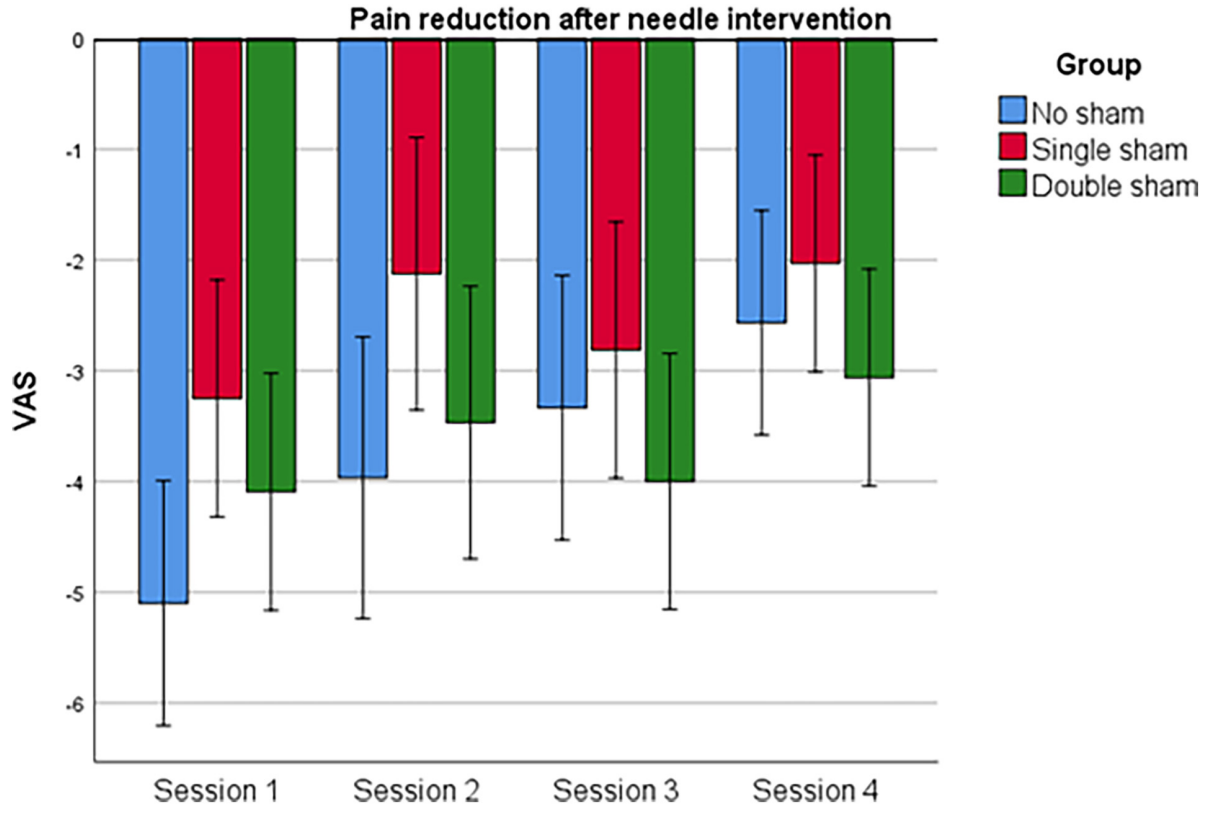


FIGURE 3
Clinical pain (tendon pain) reduction after the intervention.

treatments, verbal suggestions (40)] that enhance placebo effects and avoid nocebo effects (2, 41).

In this context, it has been shown that individuals with low back pain who received an intense briefing on the adverse side effects of acupuncture tended to exhibit a higher adverse side effect score compared to participants who received a regular adverse side effect briefing (42). However, other studies did not find a significant effect of patient expectations on the short-term effects of DN on pain intensity and pain-inducing stimulus intensities in people with neck pain; (43) or showed that DN treatment can produce beneficial effects on neck pain and tissue mechanosensitivity, regardless of whether participants received a positive, negative, or neutral verbal stimulus before treatment (44).

All participants in the current study experienced post-DN soreness that did not influence treatment outcomes. Interestingly, participants were not very concerned about post-needling soreness as long as their clinical pain complaint decreased. Therefore, it seems that briefings about treatment in routine care might not be as important as previously thought (42). Other variables, such as previous therapeutic experiences (31) or patient satisfaction, might also be important for clinically managing placebo and nocebo effects, as these are factors that can impact the outcome of rehabilitation (45). Indeed, according to several double-blind trials testing pain treatments, the placebo effect can be similar to specific treatment effects (9). In summary, current research on placebo effects indicates that the ethical enhancement of a placebo without using placebos or misinforming patients is feasible and ethical.

4.4 Limitations

This study did not control for demand characteristics, (46) potentially influencing results as participants may have guessed evaluator's expectations. Including measures of psychological factors such as fear, emotional stress, catastrophizing, and participants' satisfaction or subjective perception of improvement as indirect measures of the expectations, would have strengthened the study design. This would have allowed ascribing the consistent placebo and nocebo effects found to specific contextual factors. Future studies should explore placebo and nocebo effects in other needle-based techniques for the treatment of musculoskeletal pain.

5 Conclusion

The results of this research show that needling therapies for individuals with patellar tendinopathy are prone to elicit placebo and nocebo effects regarding clinical and needling-related pain, respectively. Future studies involving participants with musculoskeletal painful disorders should incorporate placebo-controlled designs and monitor both clinical and needling-related pain during the treatment period. Additionally, given the clear presence of these effects, physiotherapists and musculoskeletal clinicians are encouraged to delve into the knowledge of placebo and nocebo to better manage their patients with tendinopathies.

Data availability statement

The original contributions presented in this study are included in this article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (C.P.—C.I. PI15/0017). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

VD-G: Conceptualization, Funding acquisition, Investigation, Resources, Writing—original draft, Writing—review and editing. DP-M: Validation, Writing—original draft, Writing—review and editing. JB-A: Conceptualization, Investigation, Visualization, Writing—review and editing. PB-L: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing—original draft, Writing—review and editing. ML-P: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing—original draft, Writing—review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of the article. VD-G, JB-A, PB-L, and ML-R are members of the research group MOTUS supported by "Gobierno de Aragón" (n. B60_23D). Julia Blasco-Abadía is supported by the Grant PIF 2022-2026 from "Gobierno de Aragón". The funders did not have any role in the study.

Conflict of interest

The reviewer MG-A declared a shared affiliation, with no collaboration, with one of the authors DP-M to the handling editor at the time of the review.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1381515/full#supplementary-material

References

1. Cieza A, Causey K, Kamenov K, Hanson SW, Chatterji S, Vos T. Global estimates of the need for rehabilitation based on the global burden of disease study 2019: A systematic analysis for the global burden of disease study 2019. *Lancet.* (2021) 396:2006–17. doi: 10.1016/s0140-6736(20)32340-0

2. Testa M, Rossettini G. Enhance placebo, avoid nocebo: How contextual factors affect physiotherapy outcomes. *Manual Ther.* (2016) 24:65–74. doi: 10.1016/j.math.2016.04.006

3. Zou K, Wong J, Abdullah N, Chen X, Smith T, Doherty M, et al. Examination of overall treatment effect and the proportion attributable to contextual effect in osteoarthritis: Meta-analysis of randomised controlled trials. *Ann Rheum Dis.* (2016) 75:1964–70. doi: 10.1136/annrheumdis-2015-208387

4. Meeuwis SH, van Middendorp H, van Laarhoven AIM, van Leijenhorst C, Pacheco-Lopez G, Lavrijsen APM, et al. Placebo and nocebo effects for itch and itch-related immune outcomes: A systematic review of animal and human studies. *Neurosci Biobehav Rev.* (2020) 113:325–37. doi: 10.1016/j.neubiorev.2020.03.025

5. Wang Y, Chan E, Dorsey SG, Campbell CM, Colloca L. Who are the placebo responders? A cross-sectional cohort study for psychological determinants. *Pain.* (2022) 163:1078–90. doi: 10.1097/j.pain.0000000000002478

6. Blasini M, Corsi N, Klinger R, Colloca L. Nocebo and pain: An overview of the psychoneurobiological mechanisms. *Pain Rep.* (2017) 2:e585. doi: 10.1097/pr9.0000000000000585

7. Chavarria V, Vian J, Pereira C, Data-Franco J, Fernandes BS, Berk M, et al. The placebo and nocebo phenomena: Their clinical management and impact on treatment outcomes. *Clin Ther.* (2017) 39:477–86. doi: 10.1016/j.clinthera.2017.01.031

8. Rossettini G, Geri T, Palese A. What physiotherapists specialized in orthopedic manual therapy know about nocebo-related effects and contextual factors: Findings from a national survey. *Front Psychol.* (2020) 11:582174. doi: 10.3389/fpsyg.2020.582174

9. Colloca L, Barsky AJ. Placebo and nocebo effects. *N Engl J Med.* (2020) 382:554–61. doi: 10.1056/NEJMra1907805

10. Bialosky JE, George SZ, Horn ME, Price DD, Staud R, Robinson ME. Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *J Pain.* (2014) 15:136–48. doi: 10.1016/j.jpain.2013.10.005

11. Bishop MD, Mintken PE, Bialosky JE, Cleland JA. Patient expectations of benefit from interventions for neck pain and resulting influence on outcomes. *J Orthop Sports Phys Ther.* (2013) 43:457–65. doi: 10.2519/jospt.2013.4492

12. Riley SP, Bialosky J, Cote MP. Thoracic spinal manipulation for musculoskeletal shoulder pain: Can an instructional set change patient expectation and outcome? *Manual Ther.* (2015) 20:469–74. doi: 10.1016/j.math.2014.11.011

13. Rossettini G, Palese A, Geri T, Fiorio M, Colloca L, Testa M. Physical therapists' perspectives on using contextual factors in clinical practice: Findings from an Italian national survey. *PLoS One.* (2018) 13:e0208159. doi: 10.1371/journal.pone.0208159

14. Saueressig T, Owen PJ, Pedder H, Arora NK, Simons M, Kaczorowski S, et al. The importance of context (placebo effects) in conservative interventions for musculoskeletal pain: A systematic review and meta-analysis of randomized controlled trials. *Eur J Pain.* (2023) 28:675–704. doi: 10.1002/ejp.2222

15. Cashin AG, McAuley JH, Lamb SE, Lee H. Disentangling contextual effects from musculoskeletal treatments. *Osteoarthrit Cartil.* (2021) 29:297–9. doi: 10.1016/j.joca.2020.12.011

16. Cashin AG, Lee H, Bagg MK, O'Hagan E, Traeger AC, Kamper SJ, et al. A systematic review highlights the need to improve the quality and applicability of trials of physical therapy interventions for low back pain. *J Clin Epidemiol.* (2020) 126:106–15. doi: 10.1016/j.jclinepi.2020.06.025

17. Romero-Morales C, Bravo-Aguilar M, Abuín-Porras V, Almazán-Polo J, Calvo-Lobo C, Martínez-Jiménez EM, et al. Current advances and novel research on minimal invasive techniques for musculoskeletal disorders. *Dis Mon.* (2021) 67:101210. doi: 10.1016/j.disamonth.2021.101210

18. Gómez-Chiguano GF, Navarro-Santana MJ, Cleland JA. Effectiveness of ultrasound-guided percutaneous electrolysis for musculoskeletal pain: A systematic review and meta-analysis. *Pain Med.* (2021) 22:1055–71. doi: 10.1093/pm/pnaa342

19. Valera-Garrido F, Minaya-Muñoz F, Medina-Mirapeix F. Ultrasound-guided percutaneous needle electrolysis in chronic lateral epicondylitis: Short-term and long-term results. *Acupunct Med.* (2014) 32:446–54. doi: 10.1136/acupmed-2014-010619

20. Brady S, McEvoy J, Dommerholt J, Doody C. Adverse events following trigger point dry needling: A prospective survey of chartered physiotherapists. *J Man Manip Ther.* (2014) 22:134–40. doi: 10.1179/2042618613y.0000000044

21. Aslaksen PM, Lyby PS. Fear of pain potentiates nocebo hyperalgesia. *J Pain Res.* (2015) 8:703–10. doi: 10.2147/jpr.S91923

22. McLenon J, Rogers MAM. The fear of needles: A systematic review and meta-analysis. *J Adv Nurs.* (2019) 75:30–42. doi: 10.1111/jan.13818

23. Fernández-Rodríguez T, Fernández-Rolle Á, Truyols-Domínguez S, Benítez-Martínez JC, Casaña-Granell J. Prospective randomized trial of electrolysis for chronic plantar heel pain. *Foot Ankle Int.* (2018) 39:1039–46. doi: 10.1177/1071100718773998

24. López-Royo MP, Ríos-Díaz J, Galán-Díaz RM, Herrero P, Gómez-Trullén EM. A comparative study of treatment interventions for patellar tendinopathy: A randomized controlled trial. *Arch Phys Med Rehabil.* (2021) 102:967–75. doi: 10.1016/j.apmr.2021.01.073

25. Braithwaite FA, Walters JL, Li LSK, Moseley GL, Williams MT, McEvoy MP. Blinding strategies in dry needling trials: Systematic review and meta-analysis. *Phys Ther.* (2019) 99:1461–80. doi: 10.1093/ptj/pzz111

26. Alfredson H, Pietilä T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic achilles tendinosis. *Am J Sports Med.* (1998) 26:360–6. doi: 10.1177/03635465980260030301

27. López-Royo MP, Gómez-Trullén EM, Ortiz-Lucas M, Galán-Díaz RM, Bataller-Cervero AV, Al-Boloushi Z, et al. Comparative study of treatment interventions for patellar tendinopathy: A protocol for a randomised controlled trial. *BMJ Open.* (2020) 10:e034304. doi: 10.1136/bmjopen-2019-034304

28. Challoumas D, Zouvani A, Creavin K, Murray E, Crosbie G, Ng N, et al. Determining minimal important differences for patient-reported outcome measures in shoulder, lateral elbow, patellar and Achilles tendinopathies using distribution-based methods. *BMC Musculoskelet Disord.* (2023) 24:158. doi: 10.1186/s12891-023-06261-9

29. Burton I. Interventions for prevention and in-season management of patellar tendinopathy in athletes: A scoping review. *Phys Ther Sport.* (2022) 55:80–9. doi: 10.1016/j.ptsp.2022.03.002

30. Zwerver J, Bredeweg SW, van den Akker-Scheek I. Prevalence of Jumper's knee among nonelite athletes from different sports: A cross-sectional survey. *Am J Sports Med.* (2011) 39:1984–8. doi: 10.1177/0363546511413370

31. Colloca L, Akintola T, Haycock NR. Prior therapeutic experiences, not expectation ratings, predict placebo effects: An experimental study in chronic pain and healthy participants. *Psychother Psychosom.* (2020) 89:371–8. doi: 10.1159/000507400

32. Slagers AJ, van Veen E, Zwerver J, Geertzen JHB, Reininga IHF, van den Akker-Scheek I. Psychological factors during rehabilitation of patients with Achilles or patellar tendinopathy: A cross-sectional study. *Phys Ther Sport.* (2021) 50:145–52. doi: 10.1016/j.ptsp.2021.04.010

33. Ho RST, Ho FF, Adams J, Cramer H, Leung B, Ward L, et al. Patients' perceptions on non-specific effects of acupuncture: Qualitative comparison between responders and non-responders. *Integr Med Res.* (2022) 11:100771. doi: 10.1016/j.imr.2021.100771

34. Damien J, Colloca L, Bellei-Rodriguez C, Marchand S. Pain modulation: From conditioned pain modulation to placebo and nocebo effects in experimental and clinical pain. *Int Rev Neurobiol.* (2018) 139:255–96. doi: 10.1016/bs.irn.2018.07.024

35. Musial F. Acupuncture for the treatment of pain – A mega-placebo? *Front Neurosci.* (2019) 13:1110. doi: 10.3389/fnins.2019.01110

36. Petersen GL, Finnerup NB, Colloca L, Amanzio M, Price DD, Jensen TS, et al. The magnitude of nocebo effects in pain: A meta-analysis. *Pain.* (2014) 155:1426–34. doi: 10.1016/j.pain.2014.04.016

37. Lorenz J, Hauck M, Paur RC. Cortical correlates of false expectations during pain intensity judgments–a possible manifestation of placebo/nocebo cognitions. *Brain Behav Immun.* (2005) 19:283–95. doi: 10.1016/j.bbi.2005.03.010

38. Laramée A, Léonard G, Morin M, Roch M, Gaudreault N. Neurophysiological and psychophysical effects of dry versus sham needling of the infraspinatus muscle in patients with chronic shoulder pain: A randomized feasibility study. *Arch Physiother.* (2021) 11:23. doi: 10.1186/s40945-021-00118-x

39. Colloca L. Placebo, nocebo, and learning mechanisms. *Handb Exp Pharmacol.* (2014) 225:17–35. doi: 10.1007/978-3-662-44519-8_2

40. Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet Disord.* (2018) 19:27. doi: 10.1186/s12891-018-1943-8

41. Hohenschurz-Schmidt D, Thomson OP, Rossettini G, Miciak M, Newell D, Roberts L, et al. Avoiding nocebo and other undesirable effects in chiropractic, osteopathy and physiotherapy: An invitation to reflect. *Musculoskelet Sci Pract.* (2022) 62:102677. doi: 10.1016/j.msksp.2022.102677

42. Barth J, Muff S, Kern A, Zieger A, Keiser S, Zoller M, et al. Effect of briefing on acupuncture treatment outcome expectations, pain, and adverse side effects among patients with chronic low back pain: A randomized clinical trial. *JAMA Netw Open.* (2021) 4:e2121418. doi: 10.1001/jamanetworkopen.2021.21418

43. Gallego-Sendarrubias GM, Voogt L, Arias-Buría JL, Bialosky J, Fernández-de-Las-Peñas C. Can patient expectations modulate the short-term effects of dry needling on sensitivity outcomes in patients with mechanical neck pain? A randomized clinical trial. *Pain Med.* (2022) 23:965–76. doi: 10.1093/pm/pnab134

44. Almaee Nejad F, Dommerholt J, Attarbashi Moghadam B, Shadmehr A, Khazaei Pour Z. Impact of physical therapists' instructions on function and the perception of post-dry needling soreness in mechanical cervical pain; a randomized clinical trial. *J Bodyw Mov Ther.* (2020) 24:118–23. doi: 10.1016/j.jbmt.2020.06.023

45. Iolascon G, Moretti A. Myths and truths about placebo effect in rehabilitation for musculoskeletal pain. *Adv Ther.* (2021) 38:4995–5001. doi: 10.1007/s12325-021-01894-5

46. McCambridge J, de Bruin M, Witton J. The effects of demand characteristics on research participant behaviours in non-laboratory settings: A systematic review. *PLoS One.* (2012) 7:e39116. doi: 10.1371/journal.pone.0039116

frontiers | Frontiers in Medicine

TYPE Hypothesis and Theory
PUBLISHED 10 July 2024
DOI 10.3389/fmed.2024.1433070

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OPEN ACCESS

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RECEIVED 15 May 2024
ACCEPTED 01 July 2024
PUBLISHED 10 July 2024

CITATION
Zhai T, Jiang F, Chen Y, Wang J and Feng W (2024) Advancing musculoskeletal diagnosis and therapy: a comprehensive review of trigger point theory and muscle pain patterns.
Front. Med. 11:1433070.
doi: 10.3389/fmed.2024.1433070

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Advancing musculoskeletal diagnosis and therapy: a comprehensive review of trigger point theory and muscle pain patterns

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Musculoskeletal disorders, especially chronic muscle pain, have a significant impact on public health, affecting millions worldwide. This review examines recent advancements in the diagnosis and management of myofascial pain, with a focus on the refined application of trigger point theory. This theory now incorporates an intricate model that blends biomechanical and neurophysiological mechanisms, essential for understanding the initiation and persistence of pain, and necessitating targeted therapeutic interventions. Utilizing a methodical approach, this paper categorizes muscle pain into three types: Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain, as delineated in the most recent edition of "Myofascial Pain and Dysfunction—The Trigger Point Manual." Such classification enhances diagnostic precision and therapeutic effectiveness by establishing a specific treatment protocol for each type of pain. The paper discusses the implications of various treatments, such as dry needling and manual therapy, which are informed by empirically derived trigger point charts. These charts are instrumental in pinpointing the exact locations of pain sources and customizing treatment plans. Moreover, this review critically assesses the evolving nature of trigger point charts and champions a holistic approach to pain management. It underscores the necessity of integrating biomechanics, kinesiology, and compensatory mechanisms to provide a comprehensive understanding that allows practitioners to address not only symptomatic pain but also the root causes of musculoskeletal disorders, thereby enhancing long-term patient care outcomes in clinical environments.

KEYWORDS

trigger point therapy, muscle pain patterns, myofascial pain syndrome, dry needling, musculoskeletal pain management

1 Introduction

Musculoskeletal disorders encompass a wide array of conditions that significantly impact the global population, with chronic muscle pain being a predominant issue that affects millions worldwide. These conditions not only lead to substantial personal discomfort and disability but also contribute to enormous socio-economic burdens due to healthcare costs and lost

productivity (1). Among the various underlying mechanisms of musculoskeletal pain, trigger points—hyperirritable spots in skeletal muscle that are associated with palpable nodules in taut bands—play a critical role in the development and perpetuation of pain syndromes. Trigger points are often a primary factor in the onset of chronic pain, necessitating targeted treatment strategies to mitigate their effects (2).

The management of trigger points involves several therapeutic approaches, of which dry needling and manual therapy are particularly noteworthy (3). These treatments are guided by detailed trigger point charts that map the locations and characteristic referred pain patterns associated with specific trigger points. Such charts are invaluable tools in clinical settings, enabling healthcare professionals to accurately diagnose and effectively treat the complex presentations of myofascial pain. By integrating these treatment modalities within a comprehensive care plan, practitioners can significantly improve patient outcomes by directly addressing the source of pain, thus enhancing the overall quality of life for those affected by chronic musculoskeletal conditions. "*Myofascial Pain and Dysfunction: The Trigger Point Manual*," authored by Janet Travell and David Simons, is a seminal text on myofascial pain syndrome. The book provides detailed descriptions of the locations, diagnostic techniques, and treatment strategies for myofascial trigger points, along with extensive charts that help physicians and therapists identify and address associated pains. These charts enable therapists to pinpoint trigger points linked to specific pain areas and apply manual manipulation or needling techniques to alleviate pain and improve function. However, the vast number of charts presents a memorization challenge for therapists. For example, the second edition of the manual described 255 trigger points, each associated with distinct referred pain patterns even within the same muscle, while the 2019 third edition transitioned to describing pain patterns related to muscle groups, detailing 89 muscle pain patterns with some modifications in the locations of referred pain. Recent studies have indicated that trigger points are manifestations of muscle injuries and clinical symptoms (4). Through an analysis of the muscle pain regions described in the third edition of "Myofascial Pain and Dysfunction: The Trigger Point Manual," muscle pain patterns can be classified into Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain. This classification serves to provide therapists with a rapid and precise framework for diagnosing and identifying injured muscles in the process of musculoskeletal pain rehabilitation.

The concept of trigger points was first introduced by American physician Janet Travell in 1942, who posited that these points were confined solely to the muscle belly. Her student, David Simons, expanded upon this theory by introducing the concept of "attachment trigger points" within tendons and by enhancing the precision of the trigger point maps, thereby establishing them as definitive resources in the study of trigger points (5). Trigger points typically arise from taut bands within skeletal muscles, stemming from long-standing muscle imbalances that lead to various myofascial pain syndromes. When these bands are compressed or treated with techniques such as dry needling, patients typically report characteristic radiating pain. The formation of trigger points is believed to require three criteria: a distinctly painful taut nodule, referred pain, and both local and distal muscle twitch responses upon needling and palpation (6). Simons and his colleagues hypothesized that these palpable taut bands result primarily from the excessive release of acetylcholine at neuromuscular junctions in the motor endplates, causing prolonged muscle fiber contraction, increased metabolism, and localized ischemia, which in turn trigger pain and autonomic responses, including enhanced sweating and vascular activity (7). The emergence of trigger points after muscle injury is an indicator of underlying muscle damage (8). Sensitization refers to the phenomenon where, under repeated stimulation, the nervous system's threshold for pain perception decreases and its response to pain increases (9). This phenomenon is due to local and systemic inflammatory responses triggered by trigger points, which activate and modulate pain transmission pathways in the nervous system. In the case of myofascial trigger points, localized muscle tension and microcirculatory disturbances can trigger the release of cytokines and inflammatory mediators, sensitizing peripheral nerve endings and amplifying pain signals (10). Over time, if this local sensitization is not effectively controlled and treated, it may spread to the central nervous system, leading to what is known as central sensitization. Central sensitization involves an increased activity of neurons in the dorsal horn of the spinal cord, which can respond actively even without external stimuli, further reducing the pain threshold and leading to hyper-responses to normal tactile stimuli (such as allodynia) (11). Therefore, addressing myofascial trigger points early on, preventing further sensitization of these points, and reducing the transmission of pain signals are crucial for the early management of chronic pain. Moreover, for therapists, remembering the relevant trigger points' referred pain within the muscles is essential.

Over the past few decades, the understanding of trigger point theory has evolved from a simplistic local muscle pain theory into a comprehensive model encompassing extensive biomechanical and neurophysiological mechanisms (12). The pioneering work of Janet Travell and David Simons has provided profound insights into trigger points, which are not only sources of muscle pain but also key factors in various chronic pain syndromes (13). With the emergence of further research on the mechanisms of action of trigger points, a deeper understanding of therapeutic approaches for these pain points has been developed, significantly impacting pain management practices.

This evolution of the theory has led to a more refined classification of myofascial pain, which is detailed in this paper by categorizing the pain patterns of 89 muscles as outlined in the third edition of "Myofascial Pain and Dysfunction—The Trigger Point Manual." The classification divides muscle pain into Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain, each based on their distinct pain features. These classifications are not only grounded in pathophysiology but also incorporate a deep understanding of etiology, allowing for more targeted treatment approaches. For instance, Muscle Belly Pain is commonly associated with overuse or injury, Origin-Insertion Pain relates to mechanical stress between the muscle and its attachment points, and Referred Pain involves more complex neural pathways issues. This structured approach ensures that treatment modalities are effectively aligned with the underlying causes of pain, enhancing the specificity and efficacy of interventions.

2 Muscle Belly Pain

Muscle Belly Pain, which we define as pain in the belly of the muscle, a prevalent type of muscle discomfort, is often induced by external factors such as overstretching or excessive use of the muscle belly, impacting most muscles in the human body. For example,

excessive protraction (abduction) of the scapula can overstretch the rhomboid muscles, leading to pain along the medial edge of the scapula (Figure 1); overuse of the biceps may cause anterior upper arm pain; and excessive stretching of the quadratus lumborum might result in lateral lumbar pain. Such pain patterns are frequently observed in clinical settings; however, therapists sometimes incorrectly identify the pain location as the primary cause, resulting in less than optimal treatment outcomes and recurrent patient conditions. In the management of muscle belly pain, it is crucial to understand the biomechanical relationships among muscles, including the interactions between agonist and antagonist muscles, the affected postures, and potential compensatory mechanisms. For instance, pain in the rhomboid muscles may be triggered by excessive stretching of the pectoralis minor and serratus anterior (14); pain in the quadratus lumborum could be caused by stretching of the contralateral quadratus lumborum (15); excessive shortening of the forearm supinator muscles may restrict forearm pronation. Such conditions during actions like reaching behind the back can lead to excessive internal rotation of the humerus, causing pain in the anterior shoulder. Therefore, therapists should focus not only on localized pain but also evaluate the overall functional state of the muscle group to ensure effective treatment outcomes. This can be achieved by relying on the relationships between agonist and antagonist muscles, muscle strength tests, and muscle length tests, to analyze whether there are functional issues with the muscles. Such as he semitendinosus and gluteus maximus muscles can both cause pain in the ischial tuberosity region when bending. By conducting length tests of the gluteus maximus and semitendinosus, one can analyze the relevant injury points. If the length of the semitendinosus decreases after knee flexion and the pain still persists, it may indicate an injury to the gluteus maximus; if the pain decreases, it suggests an injury to the semitendinosus. In conclusion, although many patients exhibit symptoms of localized muscle belly pain, addressing only the local issues often does not result in lasting therapeutic benefits.

Muscle Belly Pain is typically caused by overuse or excessive stretching of the muscles, but accurately diagnosing the specific source of this pain can be challenging, as the symptoms often resemble Muscle Belly Pain in surrounding muscles. Precise identification of the pain points and the specific location of discomfort requires detailed assessments of muscle function and strength. Understanding the biomechanical causes of muscle belly pain is crucial for selecting the appropriate treatment approach. For example, if the muscle pain is induced by specific movements or improper postures, appropriate physical therapy and adjustments to the way movements are performed can significantly improve the patient's symptoms. Additionally, educating patients on how to avoid activities that may trigger the pain forms an integral part of the treatment strategy.

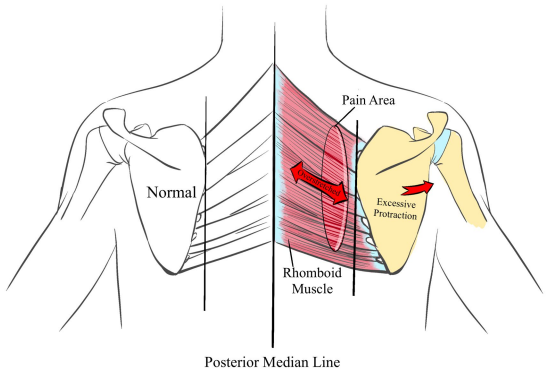

FIGURE 1
The Muscle Belly Pain in rhomboid muscles area is always associated with excessive protraction (abduction) of the scapula.

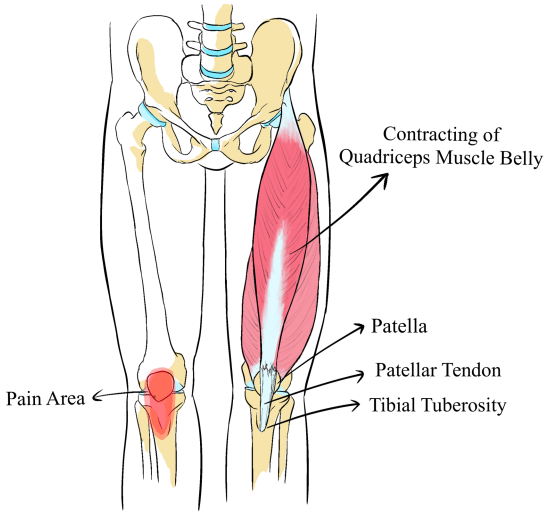

FIGURE 2
The Origin-Insertion Pain of quadriceps lead to pain extending from the patella to the tibial tuberosity.

3 Origin-Insertion Pain

We define Origin-Insertion Pain as the pain occurring at the attachment points of muscles following repeated overuse. Muscle contractions move bones by pulling on the tendons, and the repetitive contractions can easily lead to pain in their attachment areas. For instance, excessive use of the quadriceps can lead to pain extending from the patella to the tibial tuberosity (16) (Figure 2). Similarly, tennis elbow often involves the extensor carpi radialis longus, extensor carpi radialis brevis, and supinator muscles, all of which connect to the lateral epicondyle of the humerus (17). Beneath the medial malleolus, the flexor retinaculum encompasses the posterior tibial muscle, the long flexor muscle of the toes, and the long flexor muscle of the metatarsus, which likely contribute to pain in this region (18). Such pain is frequently linked to muscle overuse, where repetitive actions cause tendons to persistently pull at their bony attachment points, thereby increasing local stress. For example, chronic anterior knee pain might stem from the hyperextension and excessive strain on the quadriceps, enlarging the tibial tuberosity (19). Plantar fasciitis could result from the repeated pulling of the quadratus plantae or plantar fascia on the calcaneal tuberosity, causing heel spurs (20). de Quervain tenosynovitis may be related to friction between the sheaths of the abductor pollicis longus and the extensor pollicis brevis and the radial styloid, causing localized swelling (21). Detecting changes in these bony landmarks through palpation or imaging provides a clinical basis for evaluating muscle overuse. In clinical practice, palpating these specific areas is an effective method to determine

muscle overuse, as many symptoms are manifest at these anatomical sites.

Origin-Insertion Pain involves mechanical stress between muscles and their attachment points, making this type of pain challenging to diagnose due to its specific location. Such pain points may become inflamed due to muscle tension or minor tears, necessitating precise imaging studies and physical examinations for accurate identification. Effective treatment of Origin-Insertion Pain requires alleviating tension in the muscles and tendons to restore their normal function. Treatment modalities may include localized injections, physical therapy, or specific stretching and strengthening exercises. Proper treatment not only alleviates pain but also helps prevent future injuries.

4 Referred Pain

Referred pain, historically discussed as either visceral or somatic, is the discomfort perceived in regions distant from the source. Visceral referred pain arises from damage to internal organs, affecting areas served by the corresponding nerve roots of the sensory nerves (22). Spinal referred pain, on the other hand, stems from stimulation of structures like ligaments, intervertebral disks, and facet joints, leading to pain elsewhere (23). In the context of trigger point theory, it is posited that each muscle may exhibit a unique pattern of referred pain, although the vast number of referred pain maps implies that a single muscle could exhibit multiple referred pain manifestations. These referred pains are classified based on their origin into Peripheral Nerve Referred Pain, Same-root Nerve Radicular Pain, and Special Referred Pain, each reflecting different underlying mechanisms.

4.1 Peripheral Nerve Referred Pain

Peripheral nerve involvement in musculoskeletal pain is associated with nerves traversing within muscles. When these nerves are activated through needling or manual techniques, they cause pain to radiate to the areas they innervate. For example, damage to the iliopsoas muscle may lead to pain in the anterior thigh and groin, which cannot be fully explained by merely examining the muscle's origin and insertion points (24). However, considering the impact on nerves such as the iliohypogastric, ilioinguinal, and femoral nerves traversing the iliacus clarifies the pain pattern. The iliohypogastric nerve's abdominal branch and the ilioinguinal nerve control the groin area, while the femoral nerve covers the anterior thigh, making the resulting pain patterns more comprehensible. Similarly, damage to the anterior scalene muscle often causes referred pain to the chest's front, the inner border of the scapula, and even the thumbs and little fingers (25). This pain pattern is linked to the nerves passing behind or between the scalenes, including branches of the brachial plexus, the long thoracic nerve, the dorsal scapular nerve, the radial nerve, and the ulnar nerve (Figure 3). Consistency in the nerves running through various muscles may lead to shared pain areas, as seen with the long head of the triceps, teres minor, and teres major, which, together with the humerus, form the quadrilateral space for the axillary nerve that affects the deltoid area it innervates (26). In clinical treatment, effectively addressing related pain first involves identifying the nerves that innervate the affected area. Treatment can then proceed by needling or manually releasing the muscles through which these nerves pass, directly alleviating the pain in the targeted region.

4.2 Same Nerve Root Radicular Pain

The second type of referred muscle pain involves shared same nerve root radiation, a phenomenon where prolonged stimulation of a branch nerve can affect another branch via the same nerve root, resulting in corresponding nerve stimulation. Muscle contractions, regulated by nerve control, often coincide with functional abnormalities in the peripheral nerves. According to the theory of axonal flow, these abnormalities influence the nerve roots and subsequently radiate through the shared nerve root, affecting the corresponding dermatome area controlled by these nerves. For example, damage to the infraspinatus, innervated by the upper scapular nerve (C_5, C_6), may induce pain in the long head of the biceps brachii region at the anterior shoulder, governed by the musculocutaneous nerve (C_5, C_6, C_7). If the infraspinatus is compromised, the upper scapular nerve is impacted, altering its internal blood supply and increasing tension in the C_5 and C_6 nerve roots, which then affects the musculocutaneous nerve, leading to biceps pain. Similarly, an injury to the gluteus minimus, which influences the lateral areas of the thigh and lower leg, can cause pain in these regions (27). The gluteus minimus is controlled by the superior gluteal nerve (L_4, L_5, S_1), and the lateral parts of the thigh and lower leg are also innervated by the L_4 and L_5 nerves (Figure 4). When needling is performed in the gluteus medius and gluteus minimus, patients may report radiating pain in the lateral thigh and lower leg. This type of Same Nerve Root Radicular Pain often manifests not as pain in the muscle area through which the nerve passes but rather in the area controlled by the nerve roots, which makes it susceptible to misdiagnosis as a nerve root disorder. As previously mentioned, damage to the gluteus minimus often presents as pain in the lateral aspect of the lower leg and can be incorrectly diagnosed as conditions such as spinal stenosis or lumbar nerve root compression.

Peripheral Nerve Referred Pain involvement primarily targets the nerve trunk, which may be concentrated in a specific area or throughout the entire region innervated by the peripheral nerve. This occurs as the nerve exits the muscle, and stimulation of the muscle can lead to referred pain in the area innervated by that nerve. On the other hand, Same Nerve Root Radicular Pain associated with the same nerve root involves the nerve root itself. This type of pain emerges when there is dysfunction in the motor fibers of the nerve root, manifesting as muscular issues. Subsequently, stimulation of the affected muscles can lead to pain in the areas served by the sensory fibers of that nerve root. This pain typically encompasses a broader area and may affect multiple body parts innervated by the same nerve root.

4.3 Special Referred Pain

We define the third type of muscle referred pain as "Special Referred Pain," Which is characterized by an absence of a clear pattern or established mechanism of referral. This category includes instances

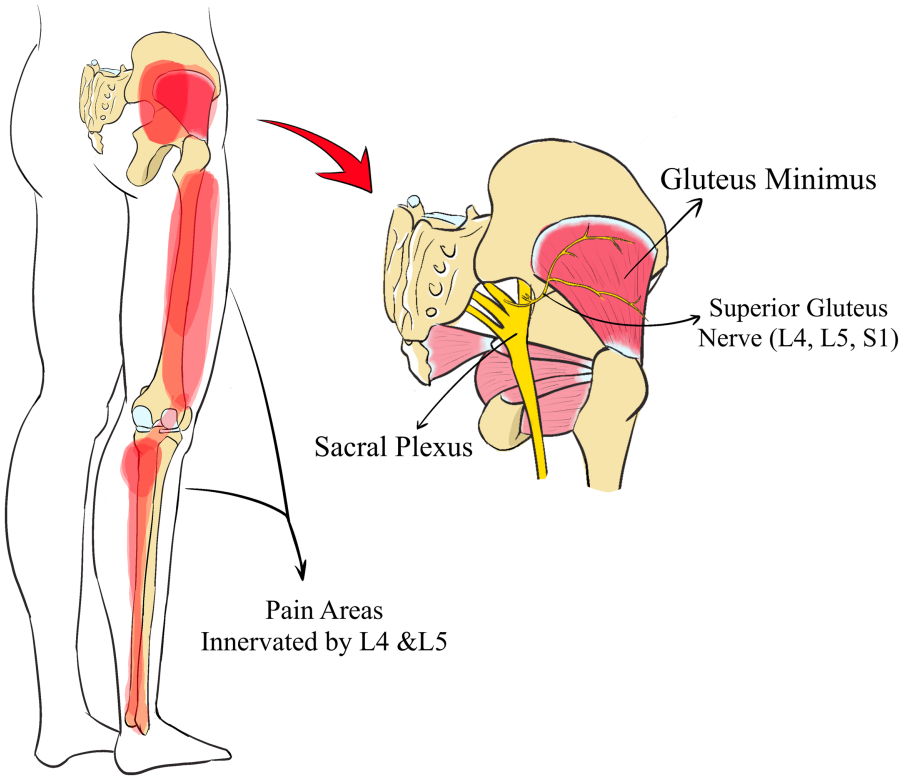

FIGURE 3
The Peripheral Nerve Referred Pain of scalene muscle.

such as an injury to the soleus muscle causing referred pain to the same side of the cheek area, an injury to the subscapularis muscle resulting in pain on the dorsal side of the wrist, and diaphragm injury leading to pain above the first rib. These examples do not conform to the conventional theories of peripheral nerve involvement or shared nerve reflexes and lack consistent patterns. As a result, they are classified under special referred pain, distinguished by their unique and not yet fully understood nature.

The diagnosis of Referred Pain is particularly complex because the pain sensation often appears at locations far from the actual trigger points. This requires physicians to have a comprehensive understanding of the pain transmission pathways related to the involved nerves and muscle groups to accurately identify the source of pain. The treatment of Referred Pain focuses on addressing the underlying neural and muscular issues and may include techniques such as dry needling, massage, and other manual therapies directly targeting the trigger points. This treatment not only requires precise diagnosis but also necessitates personalized treatment plans tailored to the specific pain patterns and the overall condition of the patient.

Statistical analysis of The third edition of "Myofascial Pain and Dysfunction: The Trigger Point Manual" presents muscle distribution and associated pain patterns. It reports that the majority of muscles manifest three primary types of pain: Muscle Belly Pain (85.4%), Origin-Insertion Pain (80.9%), and Referred Pain (59.5%) (Table 1). This detailed distribution underscores the pervasive nature of these pain patterns across different muscle groups. Regarding Referred Pain, Peripheral Nerve Referred Pain predominantly affects proximal limbs and the spine. In contrast, Same-Root Nerve Reflex pain typically occurs around the shoulders, back, pelvis, and hips, with instances in the forearm, wrist, and hands being rare. This observation supports the theoretical foundation for addressing distal joint discomfort via interventions at the spine or proximal joints. For instance, wrist pain might stem from complications in the forearm, elbow, shoulder, or cervical spine, necessitating a detailed assessment to pinpoint the exact location of the injury based on the presented pain.

5 Discussion

In recent years, trigger point theory has increasingly been recognized, though the corresponding referred pain maps remain underdeveloped. While this theory adopts a holistic approach to developing treatment plans, it neglects the influences of kinesiology, biomechanics, and compensatory mechanisms. Consequently, this article methodically categorizes muscle pain patterns into Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain. Such classification is essential for the rapid diagnosis and effective treatment of pain arising from muscle injuries in clinical environments, facilitating more precise and targeted therapeutic interventions. Our theoretical framework expands the traditional concept of myofascial trigger points to encompass a comprehensive understanding of the interactions between muscle groups and the nervous system, emphasizing holistic rather than isolated point interactions. This approach significantly improves diagnostic accuracy by accounting for nerve pathways within muscle structures, thereby enabling more precise localization of pain sources—a crucial advantage in managing

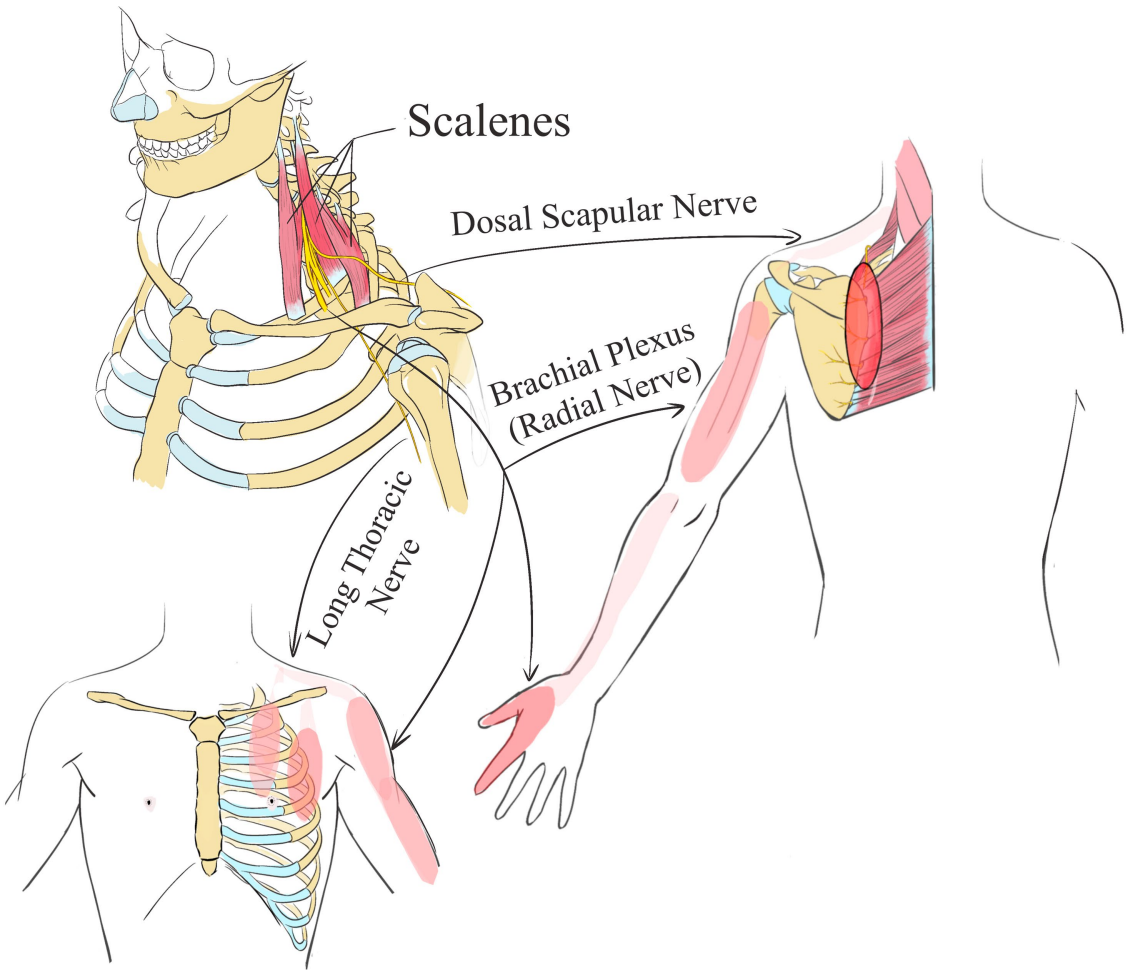

FIGURE 4
The Same Nerve Root Radicular Pain of gluteus minimus.

TABLE 1 Table of muscle pain patterns by body part.

	Number of muscles	Muscle Belly Pain	Origin-Insertion Pain	Referred Pain	Same Nerve Root Radicular Pain
				Peripheral Nerve Referred Pain	
Head, Face, and Neck	11	8	9	8	2
Upper Back and Shoulder	13	9	11	4	8
Forearm, Wrist, and Hand	18	14	8	6	0
Trunk and Pelvis	15	13	14	5	8
Hip, Thigh, and Knee	16	16	15	4	3
Calf, Ankle, and Foot	16	16	15	4	1
Total	89	76 (85.4%)	72 (80.9%)	31 (34.8%)	22 (24.7%)

complex myofascial pain where conventional methods may be inadequate. Additionally, our theory extends therapeutic strategies beyond traditional treatments such as dry needling and massage, incorporating diverse physical and rehabilitative therapies, including functional electrical stimulation and targeted exercise regimes aimed at comprehensive neuromuscular adjustment. This not only enhances treatment outcomes but also promotes effective preventative measures through a deeper understanding of muscle and nerve interactions. Moreover, it opens new research avenues into the underlying causes of myofascial pain, especially regarding the role of the nervous system, thereby facilitating the development of novel diagnostic and treatment technologies and improving patient rehabilitation outcomes.

5.1 Neuromuscular mechanisms in trigger point therapy

Trigger points, located within muscle fibers, create highly sensitive and painful areas, often due to localized ischemia and energy crises. This condition results in sustained muscle contraction knots. The continuous muscle contractions hinder blood flow, thereby reducing oxygen and nutrient delivery and impeding waste removal (28). This process leads to an accumulation of metabolic waste products such as lactic acid, enhancing pain sensitivity under hypoxic conditions. Ischemia and hypoxia activate chemoreceptors and nociceptors, which then produce and release inflammatory mediators, including prostaglandins and cytokines. These mediators sensitize or activate adjacent pain nerve endings, thus triggering pain signals. Additionally, the chemically reactive environment at the trigger point site promotes the release of neurotransmitters like serotonin and norepinephrine. These neurotransmitters not only modulate pain transmission but also contribute to the cycle of sustained muscle contraction and pain (29).

Furthermore, trigger points can exacerbate pain sensitivity through central sensitization processes. In these processes, spinal level pain neurons undergo both functional and structural changes, becoming more responsive to pain stimuli originating from trigger points. This sensitization is not confined solely to the local area but may also extend to the brain, intensifying the overall perception and experience of pain (30).

Dry Needling directly stimulates trigger points, activating local muscle fibers which then induce depolarization and muscle twitch responses. These responses help disrupt the sustained contraction within the muscle, enhance local blood flow, and decrease ischemic pain (31). Dry needling also affects pain transmission pathways in the spinal cord and brain, activating the endogenous analgesic system and releasing endorphins and other natural pain relievers (32). Massage alleviates muscle tension by applying manual pressure and kneading to trigger points, which improves blood circulation and promotes the elimination of metabolic waste (13). The mechanical stimulation delivered during massage transmits signals through mechanoreceptors, inhibiting pain signal transmission and providing analgesic effects. Additionally, tactile stimulation during massage activates the body's endogenous analgesic mechanisms, further enhancing pain relief (33). Electrical Stimulation stimulates muscles and nerves with electrical currents, triggering muscle contractions and nerve activation (34). It disrupts pain signal transmission and inhibits pain perception through the gate control theory. Electrical stimulation also elevates pain thresholds, activates the endogenous analgesic system, and promotes the release of pain-relieving substances (35).

These therapeutic techniques underscore the extensive neuromuscular interactions involved in treating trigger points, emphasizing the necessity of understanding muscle referred pain from a neurological perspective.

5.2 Completeness of trigger point charts

Trigger point charts represent a form of empirical medicine, mainly developed by injecting a 2% saline solution and anesthetics into trigger points and subsequently refining the referred pain pathways based on patient descriptions (28). However, this approach does not eliminate the subjectivity of participants or the potential influence of operators when patients are unable to specify their pain locations precisely. The trigger point charts are continuously evolving; for instance, whereas the pain pattern for the diaphragm in the second edition was localized only to the diaphragm and rib area, the third edition extends this to include pain above the first rib. Additionally, the second edition lacked a pain map for the sternocleidomastoid affecting the lateral and anterior neck areas, which was included in the third edition. Clinically, discrepancies with the trigger point charts are common, such as when needling the iliopsoas at the lesser trochanter might lead patients to experience referred pain to the groin, anterior thigh, and inner thigh—areas not described in the trigger point charts. Similarly, needling the piriformis muscle may cause an electric shock sensation extending from the posterior thigh to the sole of the foot, which are areas not depicted in the maps. Moreover, needling the internal and external obturator muscles often results in patients reporting radiating pain in the inner thigh, controlled by the obturator nerve, though the maps indicate radiating pain above the hamstring on the posterior thigh. These examples demonstrate that the trigger point maps are not yet flawless and do not comprehensively represent muscle pain patterns, necessitating ongoing refinement of referred pain maps. Nevertheless, based on the systematic and predictable muscle pain patterns of Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain outlined in this article, it is feasible to develop muscle pain pattern charts that provide a theoretical basis for clinicians to diagnose injured muscles based on the location of a patient's pain, thereby enhancing clinical efficiency.

5.3 Limitations of trigger point theory

Trigger point theory suggests that muscle injury is the primary source of pain, primarily concentrating on local muscle dynamics, yet often disregards the impacts of biomechanics, kinesiology, and compensatory mechanisms on the human body. While manual and dry needling therapies effectively alleviate most pain, recurrence is frequent, as these treatments fail to address the root causes of muscle injuries. For example, treating pain along the medial border of the scapula typically involves needling the rhomboid muscles or the neck area. The third edition of the relevant manual advises treatment of the scalene and levator scapulae muscles due to the passage of the dorsal scapular nerve, a branch of the brachial plexus, through these muscles. However, such an approach often overlooks essential biomechanics and kinesiology. Pain in the rhomboid muscle area usually results from scapular abduction, which over-stretches the medial muscles, primarily caused by the tension and pulling of the serratus anterior and pectoralis minor muscles. Consequently, treatment should primarily target these muscles instead of merely addressing the pain in the dorsal area. Similarly, pain at the front of the knee from a quadriceps injury should prompt consideration of the iliopsoas' weakness and compensatory hip flexion by the rectus femoris, or an anterior pelvic tilt leading to knee hyperextension. Thus, clinical application of trigger point theory in diagnosing muscle injuries should incorporate an understanding of biomechanics, kinesiology, and compensatory processes, as the underlying causes of local muscle damage are often intricate and necessitate a comprehensive clinical approach. Additionally, chronic musculoskeletal pain is usually not caused by a single trigger point or muscle issue but involves a complex interplay of biological, psychological, and social factors. Biologically,

the interactions among nerves, muscles, bones, and soft tissues, as well as potential degenerative changes, form the basis of pain. Psychological factors such as stress, anxiety, and depression play significant roles in pain perception and the chronicity of the condition. Social factors, including occupational stress and lifestyle habits, also impact the progression and severity of the pain. This multifactorial nature necessitates the adoption of more comprehensive and personalized treatment strategies in future clinical practice (36).

5.4 The importance of muscle pain patterns in clinical diagnosis and treatment

In the assessment of musculoskeletal pain, conducting extensive specialized examinations is crucial. However, novice therapists might overlook certain influential factors or rare causes during these assessments, which can lead to missed or incorrect diagnoses. By precisely analyzing the patient's described area of pain and correlating it with established muscle pain patterns—Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain—it becomes possible to swiftly pinpoint the specific muscle responsible for the pain. This approach also aids in assessing the severity of the muscle injury based on the results of specialized examinations, thereby facilitating effective treatment measures that yield positive clinical outcomes. Modern pain treatment requires therapists to not only focus on localized symptoms but also to consider the origins of pain from a holistic perspective. The pain patterns of Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain not only address local symptoms but also illustrate how pain can spread from proximal to distal parts of the body. Research indicates that approximately 85% of referred pain propagates from proximal to distal locations (37). For example, pain in the lateral epicondyle of the humerus may stem from issues in the triceps or supraspinatus muscles (38); pain on the outer side of the calf may result from damage to the piriformis muscle (39). Viewing the upper limbs and cervical spine as one integrated system, and the lumbar spine and lower limbs as another, highlights the critical interaction between muscles within these systems for understanding pain. Therefore, acknowledging the overall transmission of pain in the diagnosis and treatment of chronic pain is essential, as it facilitates a more comprehensive approach to addressing pain issues.

5.5 The importance of comprehensive assessment for pain

The evaluation of pain in patients should not focus solely on individual muscles or trigger points, but instead incorporate a series of integrated assessment strategies to thoroughly analyze the patient's movement and biomechanical properties. Firstly, movement assessment forms the core of functional evaluation. By observing patients performing specific movements or daily activities, we can identify potentially harmful movement patterns that may cause or exacerbate pain. For instance, patients might be asked to perform squats, walk, or engage in other specific activities to observe muscle coordination, joint mobility, and pain trigger points during these movements (31). Next, biomechanical assessment aids in understanding how a patient's physical structure impacts their pain. This involves analyzing body symmetry, joint alignment, and the balance between muscle strength and flexibility. Through detailed assessment of these factors, we can identify structural and functional issues that contribute to pain, such as excessive muscle tension, uneven joint pressure, or instability. Additionally, we consider other relevant factors, including the functional status of the nervous system and psychosocial factors, which can affect a patient's perception of pain and response to treatment (40). By utilizing neurofunctional tests and psychological assessment tools, we can gain a more comprehensive understanding of the multidimensional complexity of pain and devise more effective treatment strategies. During these assessments, we employ a variety of tools and technologies, including but not limited to dynamic electronic devices, pressure sensors, and visual analysis software. These tools enable us to precisely measure and record data during the assessment process, providing quantitative feedback to help optimize treatment plans.

In summary, functional assessment is a dynamic and interactive process that requires a holistic consideration from multiple perspectives to deeply understand and address pain issues. Through this approach, we can offer patients personalized treatment plans that not only alleviate pain but also enhance their overall function and quality of life.

5.6 Integrated multidisciplinary strategies for chronic pain management

Chronic pain represents a multifaceted clinical challenge that involves intricate interplays between biological, psychological, and sociological factors (36). Effective management of chronic pain requires the synergistic integration of diverse professional expertise, including that of physical therapists, neurologists, psychologists, orthopedic surgeons, rehabilitation specialists, and pain management clinicians. Such collaborative efforts enable a comprehensive assessment of the root causes of pain, facilitating the formulation of tailored treatment strategies designed to optimize patient outcomes.

Critical to this approach is the meticulous assessment of trigger point pain, which necessitates accurate localization of pain points, characterization of their nature, and evaluation of their impact on the patient's quality of life (41). This assessment process encompasses an extensive collection of medical history, thorough physical examinations, detailed functional assessments, and comprehensive neurological evaluations. The multidisciplinary treatment modalities for addressing trigger point pain might include physical therapy interventions such as dry needling, thermotherapy, cryotherapy, and electrical stimulation; pharmacological management using anti-inflammatory agents, muscle relaxants, or antidepressants; psychological interventions, notably cognitive behavioral therapy; and rehabilitation programs that feature personalized exercise regimens and lifestyle adjustments. Additionally, educational and self-management strategies are employed to empower patients (42).

This cohesive and coordinated treatment paradigm not only directly targets the sources of pain but also significantly aids patients in navigating the psychological and social complexities associated with chronic pain. By leveraging the combined expertise of a multidisciplinary team, the effectiveness of the therapeutic interventions is markedly enhanced, offering patients a comprehensive pathway toward sustained recovery. This approach is aligned with the principles of patient-centered care, which prioritize individual health

needs and preferences in the design and implementation of healthcare strategies.

5.7 Summary

Categorizing muscle pain into Muscle Belly Pain, Origin-Insertion Pain, and Referred Pain not only enhances the efficiency of diagnosing and treating musculoskeletal pain but also lays a theoretical foundation for the further development of trigger point theory and charts. Additionally, considering a variety of factors that contribute to muscle injuries is crucial for managing chronic pain, which aids in comprehensively addressing pain issues and promotes overall advancements in musculoskeletal medicine.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

TZ: Writing – original draft. FJ: Methodology, Visualization, Writing – review & editing. YC: Writing – review & editing. JW: Writing – review & editing. WF: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Scientific Research Project of the Second Rehabilitation Hospital of Shanghai (Y2023-02).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Guan SY, Zheng JX, Sam NB, Xu S, Shuai Z, Pan F. Global burden and risk factors of musculoskeletal disorders among adolescents and young adults in 204 countries and territories, 1990-2019. *Autoimmun Rev*. (2023) 22:103361. doi: 10.1016/j.autrev.2023.103361

2. Lam C, Francio VT, Gustafson K, Carroll M, York A, Chadwick AL. Myofascial pain - a major player in musculoskeletal pain. *Best Pract Res Clin Rheumatol*. (2024):101944. doi: 10.1016/j.berh.2024.101944

3. Urits I, Charipova K, Gress K, Schaaf AL, Gupta S, Kiernan HC, et al. Treatment and management of myofascial pain syndrome. *Best Pract Res Clin Anaesthesiol*. (2020) 34:427–48. doi: 10.1016/j.bpa.2020.08.003

4. Vadasz B, Gohari J, West DW, Grosman-Rimon L, Wright E, Ozcakar L, et al. Improving characterization and diagnosis quality of myofascial pain syndrome: a systematic review of the clinical and biomarker overlap with delayed onset muscle soreness. *Eur J Phys Rehabil Med*. (2020) 56:469–78. doi: 10.23736/S1973-9087.20.05820-7

5. Lavelle ED, Lavelle W, Smith HS. Myofascial trigger points. *Med Clin North Am*. (2007) 91:229–39. doi: 10.1016/j.mcna.2006.12.004

6. Fernández-de-las-Peñas C, Dommerholt J. International consensus on diagnostic criteria and clinical considerations of myofascial trigger points: a Delphi study. *Pain Med*. (2018) 19:142–50. doi: 10.1093/pm/pnx207

7. Gerwin RD. A new unified theory of trigger point formation: failure of pre- and post-synaptic feedback control mechanisms. *Int J Mol Sci*. (2023) 24:8142. doi: 10.3390/ijms24098142

8. Plaut S. Scoping review and interpretation of myofascial pain/fibromyalgia syndrome: An attempt to assemble a medical puzzle. *PLoS One*. (2022) 17:e0263087. doi: 10.1371/journal.pone.0263087

9. Tinnirello A, Mazzoleni S, Santi C. Chronic pain in the elderly: mechanisms and distinctive features. *Biomol Ther*. (2021) 11:1256. doi: 10.3390/biom11081256

10. Steel SJ, Robertson CE, Whealy MA. Current understanding of the pathophysiology and approach to tension-type headache. *Curr Neurol Neurosci Rep*. (2021) 21:56. doi: 10.1007/s11910-021-01138-7

11. Brazenor GA, Malham GM, Teddy PJ. Can central sensitization after injury persist as an autonomous pain generator? A comprehensive search for evidence. *Pain Med*. (2022) 23:1283–98. doi: 10.1093/pm/pnab319

12. Duarte FCK, West DWD, Linde LD, Hassan S, Kumbhare DA. Re-examining myofascial pain syndrome: toward biomarker development and mechanism-based diagnostic criteria. *Curr Rheumatol Rep*. (2021) 23:69. doi: 10.1007/s11926-021-01024-8

13. Galasso A, Urits I, An D, Nguyen D, Borchart M, Yazdi C, et al. A comprehensive review of the treatment and management of myofascial pain syndrome. *Curr Pain Headache Rep*. (2020) 24:43. doi: 10.1007/s11916-020-00877-5

14. Sağlam G, Telli H. The prevalence of scapular dyskinesia in patients with back, neck, and shoulder pain and the effect of this combination on pain and muscle shortness. Sırt, boyun ve omuz ağrısı olan hastalarda skapular diskinezi prevalansı ve bu kombinasyonun ağrı ve kas kısalığı üzerine etkisi. *Agri*. (2022) 34:100–8. doi: 10.14744/agri.2022.87059

15. Cozacov R, Minerbi A, Haddad M, Vulfsons S. Differential sensitization of muscle versus fascia in individuals with low Back pain. *Bioengineering (Basel)*. (2022) 9:440. doi: 10.3390/bioengineering9090440

16. Ma YT, Li LH, Han Q, Wang XL, Jia PY, Huang QM, et al. Effects of trigger point dry needling on neuromuscular performance and pain of individuals affected by patellofemoral pain: a randomized controlled trial. *J Pain Res*. (2020) 13:1677–86. doi: 10.2147/JPR.S240376

17. Nimura A, Shimura H, Hoshika S, Fukai A, Akita K. Elbow anatomy in perspective of joint capsule and surrounding aponeuroses: a narrative review. *JSES Int*. (2024) 8:654–60. doi: 10.1016/j.jseint.2024.01.006

18. Sanghvi D, Agrawal S. Medial ankle pain In: M Davies, S James and R Botchu, editors. Imaging of the foot and ankle. Medical radiology. Cham: Springer (2023)

19. Nakase J, Goshima K, Numata H, Oshima T, Takata Y, Tsuchiya H. Precise risk factors for Osgood-Schlatter disease. *Arch Orthop Trauma Surg*. (2015) 135:1277–81. doi: 10.1007/s00402-015-2270-2

20. Llurda-Almuzara L, Labata-Lezaun N, Meca-Rivera T, Navarro-Santana MJ, Cleland JA, Fernández-de-las-Peñas C, et al. Is dry needling effective for the Management of Plantar Heel Pain or plantar fasciitis? An updated systematic review and Meta-analysis. *Pain Med*. (2021) 22:1630–41. doi: 10.1093/pm/pnab114

21. Ferrara PE, Codazza S, Cerulli S, Maccauro G, Ferriero G, Ronconi G. Physical modalities for the conservative treatment of wrist and hand's tenosynovitis: a systematic review. *Semin Arthritis Rheum*. (2020) 50:1280–90. doi: 10.1016/j.semarthrit.2020.08.006

22. Pacheco-Carroza EA. Visceral pain, mechanisms, and implications in musculoskeletal clinical practice. *Med Hypotheses*. (2021) 153:110624. doi: 10.1016/j.mehy.2021.110624

23. Jin Q, Chang Y, Lu C, Chen L, Wang Y. Referred pain: characteristics, possible mechanisms, and clinical management. *Front Neurol*. (2023) 14:1104817. doi: 10.3389/fneur.2023.1104817

24. Lifshitz L, Bar Sela S, Gal N, Martin R, Fleitman KM. Iliopsoas the hidden muscle: anatomy, diagnosis, and treatment. *Curr Sports Med Rep*. (2020) 19:235–43. doi: 10.1249/JSR.0000000000000723

25. Ferrante MA, Ferrante ND. The thoracic outlet syndromes: part 2. The arterial, venous, neurovascular, and disputed thoracic outlet syndromes. *Muscle Nerve*. (2017) 56:663–73. doi: 10.1002/mus.25535

26. Bertelli JA, Goklani MS, Gasparelo KR, Seltser A. Transdeltoid approach to axillary nerve repair: anatomical study and case series. *J Hand Surg Am*. (2023) 48:82.e1–9. doi: 10.1016/j.jhsa.2021.09.017

27. Skorupska E, Dybek T, Rychlik M, Jokiel M, Dobrakowski P, Szczerba A, et al. A potential objective sign of central sensitization: referred pain elicited by manual gluteus Minimus muscle exploration is coincident with pathological autonomic response provoked by noxious stimulation. *Pain Res Manag*. (2023) 2023:4030622–11. doi: 10.1155/2023/4030622

28. Appasamy M, Lam C, Alm J, Chadwick AL. Trigger point injections. *Phys Med Rehabil Clin N Am*. (2022) 33:307–33. doi: 10.1016/j.pmr.2022.01.011

29. Money S. Pathophysiology of trigger points in myofascial pain syndrome. *J Pain Palliat Care Pharmacother*. (2017) 31:158–9. doi: 10.1080/15360288.2017.1298688

30. Fernández-de-las-Peñas C, Dommerholt J. Myofascial trigger points: peripheral or central phenomenon? *Curr Rheumatol Rep*. (2014) 16:395. doi: 10.1007/s11926-013-0395-2

31. Gattie E, Cleland JA, Snodgrass S. The effectiveness of trigger point dry needling for musculoskeletal conditions by physical therapists: a systematic review and Meta-analysis. *J Orthop Sports Phys Ther*. (2017) 47:133–49. doi: 10.2519/jospt.2017.7096

32. Fernández-de-Las-Peñas C, Nijs J. Trigger point dry needling for the treatment of myofascial pain syndrome: current perspectives within a pain neuroscience paradigm. *J Pain Res*. (2019) 12:1899–911. doi: 10.2147/JPR.S154728

33. Lu W, Li J, Tian Y, Lu X. Effect of ischemic compression on myofascial pain syndrome: a systematic review and meta-analysis. *Chiropr Man Therap*. (2022) 30:34. doi: 10.1186/s12998-022-00441-5

34. Moro MZ, de Oliveira Vidal EI, Pinheiro Módolo NS, Bono Fukushima F, Moreira de Barros GA. Dry needling, trigger point electroacupuncture and motor point electroacupuncture for the treatment of myofascial pain syndrome involving the trapezius: a randomised clinical trial. *Acupunct Med*. (2024) 42:3–13. doi: 10.1177/09645284231207865

35. Ahmed S, Haddad C, Subramaniam S, Khattab S, Kumbhare D. The effect of electric stimulation techniques on pain and tenderness at the myofascial trigger point: a systematic review. *Pain Med*. (2019) 20:1774–88. doi: 10.1093/pm/pny278

36. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet*. (2021) 397:2082–97. doi: 10.1016/S0140-6736(21)00393-7

37. Yungui J. Illustrated treatment of myofascial trigger points. China: Heji Book Publishing (2012). 7 p.

38. Navarro-Santana MJ, Sanchez-Infante J, Gómez-Chiguano GF, Cleland JA, López-de-Uralde-Villanueva I, Fernández-de-las-Peñas C, et al. Effects of trigger point dry needling on lateral epicondylalgia of musculoskeletal origin: a systematic review and meta-analysis. *Clin Rehabil*. (2020) 34:1327–40. doi: 10.1177/0269215520937468

39. Skorupska E, Rychlik M, Samborski W. Intensive vasodilatation in the sciatic pain area after dry needling. *BMC Complement Altern Med*. (2015) 15:72. doi: 10.1186/s12906-015-0587-6

40. Ramsook RR, Malanga GA. Myofascial low back pain. *Curr Pain Headache Rep*. (2012) 16:423–32. doi: 10.1007/s11916-012-0290-y

41. Parthasarathy S, Sundar S, Mishra G. Assessment of predisposing factors in myofascial pain syndrome and the analgesic effect of trigger point injections - a primary therapeutic interventional clinical trial. *Indian J Anaesth*. (2019) 63:300–3. doi: 10.4103/ija.IJA_6_19

42. Volcheck MM, Graham SM, Fleming KC, Mohabbat AB, Luedtke CA. Central sensitization, chronic pain, and other symptoms: better understanding, better management. *Cleve Clin J Med*. (2023) 90:245–54. doi: 10.3949/ccjm.90a.22019

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 29 July 2024
DOI 10.3389/fmed.2024.1404939

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RECEIVED 21 March 2024
ACCEPTED 12 July 2024
PUBLISHED 29 July 2024

CITATION
Pinilla-Fernández I, Ríos-León M, Deelchand DK, Garrido L, Torres-Llacsa M, García-García F, Vidorreta M, Ip IB, Bridge H, Taylor J and Barriga-Martín A (2024) Chronic neuropathic pain components in whiplash-associated disorders correlate with metabolite concentrations in the anterior cingulate and dorsolateral prefrontal cortex: a consensus-driven MRS re-examination. *Front. Med.* 11:1404939. doi: 10.3389/fmed.2024.1404939

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Chronic neuropathic pain components in whiplash-associated disorders correlate with metabolite concentrations in the anterior cingulate and dorsolateral prefrontal cortex: a consensus-driven MRS re-examination

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Introduction: Whiplash injury (WHI) is characterised by a forced neck flexion/extension, which frequently occurs after motor vehicle collisions. Previous studies characterising differences in brain metabolite concentrations and correlations with neuropathic pain (NP) components with chronic whiplash-associated disorders (WAD) have been demonstrated in affective pain-processing areas such as the anterior cingulate cortex (ACC). However, the detection of a difference in metabolite concentrations within these cortical areas with chronic WAD pain has been elusive. In this study, single-voxel magnetic resonance spectroscopy (MRS), following the latest MRSinMRS consensus group guidelines, was performed in the anterior cingulate cortex (ACC), left dorsolateral prefrontal cortex (DLPFC), and occipital cortex (OCC) to quantify differences in metabolite concentrations in individuals with chronic WAD with or without neuropathic pain (NP) components.

Materials and methods: Healthy individuals ($n = 29$) and participants with chronic WAD ($n = 29$) were screened with the Douleur Neuropathique 4 Questionnaire (DN4) and divided into groups without (WAD-noNP, $n = 15$) or

with NP components (WAD-NP, $n = 14$). Metabolites were quantified with LCModel following a single session in a 3 T MRI scanner within the ACC, DLPFC, and OCC.

Results: Participants with WAD-NP presented moderate pain intensity and interference compared with the WAD-noNP group. Single-voxel MRS analysis demonstrated a higher glutamate concentration in the ACC and lower total choline (tCho) in the DLPFC in the WAD-NP versus WAD-noNP group, with no intergroup metabolite difference detected in the OCC. Best fit and stepwise multiple regression revealed that the normalised ACC glutamate/total creatine (tCr) ($p = 0.01$), DLPFC n-acetyl-aspartate (NAA)/tCr ($p = 0.001$), and DLPFC tCho/tCr levels ($p = 0.02$) predicted NP components in the WAD-NP group (ACC $r^2 = 0.26$, $\alpha = 0.81$; DLPFC $r^2 = 0.62$, $\alpha = 0.98$). The normalised Glu/tCr concentration was higher in the healthy than the WAD-noNP group within the ACC ($p < 0.05$), but not in the DLPFC or OCC. Neither sex nor age affected key normalised metabolite concentrations related to WAD-NP components when compared to the WAD-noNP group.

Discussion: This study demonstrates that elevated glutamate concentrations within the ACC are related to chronic WAD-NP components, while higher NAA and lower tCho metabolite levels suggest a role for increased neuronal–glial signalling and cell membrane dysfunction in individuals with chronic WAD-NP components.

KEYWORDS

glutamate, n-acetyl-aspartate, choline, neuropathic pain, whiplash injury, anterior cingulate cortex, dorsolateral prefrontal cortex, occipital cortex

1 Introduction

Whiplash injury (WHI) is characterised by a forced flexion extension of the neck, which frequently occurs after motor vehicle collisions, and may involve damage to intervertebral joints, discs, ligaments, muscles, and nerve roots (1). Symptoms of whiplash-associated disorders (WAD) include persistent neck pain, headache, dizziness, concentration disturbance, sleeping difficulties, and fatigue (2, 3). WAD symptoms usually resolve within 3 months, but approximately 30 and 50% of participants experience chronic pain for longer than 6 months (2–6). Although WAD is characterised by regional musculoskeletal symptoms, the development of central pathophysiological mechanisms that lead to neuropathic pain (NP) descriptors and sensory changes have also been described (3, 7–9). There is a need therefore to understand the central and peripheral pathophysiological mechanisms to improve the early diagnosis and prevention of chronic WAD symptoms, including high-impact chronic NP components (6).

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive technique that enables quantification of metabolite concentration and can provide an essential insight into pathophysiological mechanisms and therapeutic targets (10–14). Quantification of metabolite concentrations within brain pain-processing areas permits a mechanistic approach to detect site-specific biochemical changes in neuronal and glial cell dysfunction and their relationship with nociceptive and neuropathic pain types (10, 13, 14). Indeed, differences in key metabolite concentrations, such as glutamate (15–17), N-acetyl-aspartate (10, 18, 19), and GABA (20, 21), have been detected with pain subtypes. Furthermore, brain MRS has been used to demonstrate the therapeutic effects of analgesic treatments (22–24) and non-invasive neuromodulation of the cortex (25, 26). Metabolite concentrations within the anterior cingulate cortex (ACC) and periaqueductal grey matter (PAG) are known to correlate with WAD-NP components and endogenous pain modulation during chronic WAD, possibly related to changes in glutamatergic and neuroinflammatory mechanisms (27). However, no general difference in metabolite concentrations has been identified within the primary motor cortex, somatosensory cortex, ACC, or PAG when compared between individuals with WAD with or without chronic pain (27, 28). Furthermore, the involvement of metabolite modulation within other key areas, such as the dorsolateral prefrontal cortex (DLPFC), during chronic WAD pain has not been previously reported (29).

The technical challenges associated with ^{1}H MRS acquisition methodology and metabolite analysis (30, 31) may explain the failure to detect subtle differences in metabolite concentrations related to chronic WAD pain. This limitation can be addressed with the use of the semi-adiabatic localisation by adiabatic selective refocusing sequence (semi-LASER) (30), single-voxel spectroscopy acquisition for specific anatomical regions (30, 31), and the development and implementation of a simulated basis set into the analysis (30). Analysis programmes available on scanner software are usually less sensitive, and therefore, expert consensus groups, such as the MRSinMRS group, recommend software that allows pre-processing, such as phase and frequency correction and final metabolite quantification (30). Furthermore, the inclusion of anatomical areas as reference areas to

assess differences in metabolite concentrations in brain areas unrelated to specific pain types is not commonly adopted (27).

This study aimed to quantify a difference in metabolite concentration levels in the brain, in participants with chronic WHI pain screened for neuropathic components, within the ACC and the left dorsolateral prefrontal cortex (DLPFC), areas known to specifically modulate pain-related affective and mood components (32–34). The secondary aim of the study was to identify key metabolites related to chronic neuropathic pain components during chronic WHI.

2 Materials and methods

2.1 Ethics statement

This study protocol was approved by the local Clinical Research Ethics Committee (Approval number #2559/674; 2021) and was conducted at the National Hospital for Paraplegics in Toledo according to the Helsinki Declaration (35).

2.2 Study participant recruitment

Participants with WAD were recruited by orthopaedic surgeons at a hospital in Toledo (Spain). The period of recruitment was between September 2021 and July 2023. All individuals screened for eligibility provided written informed consent before their inclusion in the study. No *a priori* sample size calculation was made as similar studies performed in the chronic WHI phase did not detect differences in brain metabolite concentrations in individuals with WAD general pain (27, 28).

2.3 Inclusion criteria

For participants to be eligible, they were required to meet the following conditions: (1) clinical diagnosis of acute WAD assessed within 72 h of a traffic accident; (2) present WAD with WAD grades of between II-III according to the Quebec Task Force grading system (36–38), (3) daily pain intensity of >3 rated on the 11-point numeric rating scale (NRS) reported within 1 week of injury; (4) one or more specific descriptors assessed with the DN4 questionnaire (see below); (5) more than 3 months after WHI; and (6) 18 years of age or older (39). The exclusion criteria were as follows: (1) a history of chronic pain and/or rheumatic, neurological, or psychiatric diseases; (2) diseases causing potential neural damage (e.g., diabetes, diseases of the immune system, and oncological diseases); (3) bone injuries associated with trauma and detected in the X-ray of the cervical spine; (4) previous clinical history of cervical injuries (e.g., disc herniation, osteoarthritis, and WAD), frequent headaches, and/or orofacial pain; (5) a history of cervical surgery or surgery to the upper extremity; and (6) treatment for chronic pain previously received for long periods of time (39).

2.4 Assessment of pain interference

The Brief Pain Inventory (BPI) questionnaire was used to assess the patient's perception of pain severity and its interference with several dimensions of daily life (27, 40). The pain interference scale includes pain interference related to general activity, mood, enjoyment of life, walking ability, ability to work and perform daily tasks, and relationships with other people (40, 41). BPI pain interference was calculated as a total score of the seven items (including the sleep item) and was also calculated as subscores (41) for psychological affective interference [relationships with others, enjoyment of life and mood (REM)] and physical activity interference [walking ability, general activity, and ability to work (WAW)] (41).

2.5 Assessment of NP components

2.5.1 Physician assessment

The presence of NP components was assessed using conventional physician assessment, which was considered the gold standard (39, 42). The physician assessment was performed following routine clinical practise (39), international recommendations (43–45), and the NeuPSIG neuropathic pain criteria for probable NP (45).

This evaluation included detailed history, physical examination (e.g., movement testing, clinical bedside somatosensory function testing, and general neurological and clinical testing), and appropriate diagnostic workup including pain distribution and sensory examination (43).

2.5.2 Douleur neuropathique 4 screening questionnaire

The DN4 questionnaire is a reliable tool with high discriminatory value for the identification of NP symptoms and signs (46, 47) and has proven valid for mixed pain syndromes (sensitivity: 83%; specificity: 90%) (47). The Spanish version of the DN4 with substantial inter-rater reliability (Cohen's kappa coefficients: 0.79) and internal consistency (Cronbach's α: 0.7) has been used (39, 46). This questionnaire consists of a total of 10 items (NP descriptors): 7 items are related to the quality of pain (burning, painful cold, and electric shocks) and its association with abnormal sensations (tingling, pins and needles, numbness, and itching), and 3 items are related to clinical examination in the painful area (touch hypoesthesia, pinprick hypoesthesia, and tactile allodynia). A score of 1 is given to each positive (yes) item. The total score is calculated as the sum of the 10 items, and the cutoff value to determine the presence of NP components is a total score of DN4 of ≥4 (46).

The presence of NP components using the DN4 questionnaire was determined according to the following characteristics of pain: (1) the presence of pain descriptions such as burning or hot, electric shocks or shooting, painful cold, pricking or pins and needles, pain evoked by light touching or loss of sensitivity to mechanical stimuli, or non-painful sensations such as numbness and tingling (46, 47) and (2) the presence of abnormal findings in the clinical examination such as the sensory change to mechanical stimuli (46, 47).

2.6 Brain imaging data acquisition and processing

A total of 29 healthy participants with no chronic pain and 29 participants with WHI [WAD-noNP ($n = 15$) and WAD-NP ($n = 14$)] consented to brain imaging performed with a 3 T whole body system MRI scanner (Siemens Magnetom TrioTim Syngo MR B19) with

32-channel Rx CP head coil (Siemens). MRS acquisition and analysis parameters are included as an MRSinMRS checklist (Supplementary Table S1). First, T1-weighted structural images were acquired using a three-dimensional magnetisation-prepared rapid gradient-echo (3D MPRAGE) (48) with the following parameters: 256 slices, slice thickness = 0.90 mm, TR/TE = 2300/3.01 ms, flip angle = 9°, and isotropic voxel size = 0.9 mm. The anatomical information was used for MRS voxel placement, and the images were segmented using SPM12 to determine the fractions of grey and white matter and cerebrospinal fluid volume in each region of interest (ROI) (49). The percentage grey matter for the non-injured and chronic WHI groups for each ROI was as follows: ACC:—47.9 ± 3.8% vs. 47.4 ± 4.1%, OCC: 63.4 ± 6.9% vs. 64.7 ± 3.7%, and DLPFC: 33.0 ± 6.4% vs. 32.2 ± 9.5%. These grey matter percentages facilitate discussion of neuronal or white matter differences in key metabolites detected with MRS.

Single-voxel MRS was acquired using the pulse sequence MEGA-semi-LASER SVS (CMRR Spectroscopy Package Release 2017–07, University of Minnesota: mslaser, TE = 85 ms, TR = 3,000 ms, bandwidth = 2 KHz, average of 128 scans (64 scans for edit-off and 64 for edit-on), 2,048 data points, and total scan time = 10.8 min per ROI) with a field strength of 3 T. A longer TE time was adopted to optimise GABA + quantification with the MEGA-semi-LASER sequence (50, 51). The centre frequency was −1.7 ppm, and the shimming method was achieved using the Siemens shim "Brain" application (System 3D-GRE). An unsuppressed water reference was acquired, thus the water suppression method used was VAPOR with an optional embedded outer volume suppression (OVS) to suppress water and improve the localisation of the volume of interest (VOI).

Voxels were positioned manually in the ROIs in the axial plane by well-trained technicians with many years of experience with a 3 T scanner for MRS under the supervision of a radiologist experienced in the identification of anatomical landmarks (52). MRS acquisition of spectra within each ROI was always in the same order. The first voxel ($35 \times 35 \times 10\ mm^3$) was placed in the anterior cingulate cortex (ACC) (Figure 1A), the second voxel ($20 \times 20 \times 20\ mm^3$) was placed in the occipital lobe (OCC) (Figure 1B), and the third voxel ($20 \times 20 \times 40\ mm^3$) was placed in the left dorsolateral prefrontal cortex (DLPFC) (Figure 1C). Voxel size was based on previous studies (26, 27). MRS voxels were first registered to the T1-anatomical space and segmented (grey matter, white matter, and CSF) using SPM12 (53, 54). In this study, spectra were acquired from the DLPFC in a smaller cohort (WAD-noNP, $n = 13$, WAD-NP $n = 17$) compared to the number of individuals with spectra obtained from the ACC and OCC (WAD-noNP $n = 29$, WAD-NP $n = 29$). During the MRS data acquisition, participants were not given specific instructions.

All MRS spectra (see Figure 1D as an example) were obtained in DICOM (.IMA) format and processed using MRspa version 1.5f (55), which runs with MATLAB R2022b (56). For GABA + quantification, MRS data were obtained as the difference between two separate measurements (64 spectra for each edit-on and edit-off). The MRspa freeware spectral processing and analysis package was used in conjunction with programs SPM12 and LCModel version 6.3-1R (for fitting and quantification of metabolites). SPM12 and LCModel interface with MRspa (53, 54, 56, 57). Frequency and phase corrections were performed followed by eddy current correction. The resulting summed semi-LASER spectra were fitted using LCModel and were scaled to water. Final GABA+ concentration was calculated from the edited spectra by calculating the difference between edit-on and edit-off spectra, while the rest of the metabolites were fitted from the edit-off spectra.

The basis set file was created specifically for our sequence MEGA-semi-LASER SVS by Dr. Deelchand from the Center for Magnetic Resonance Research at the University of Minnesota. No macromolecules

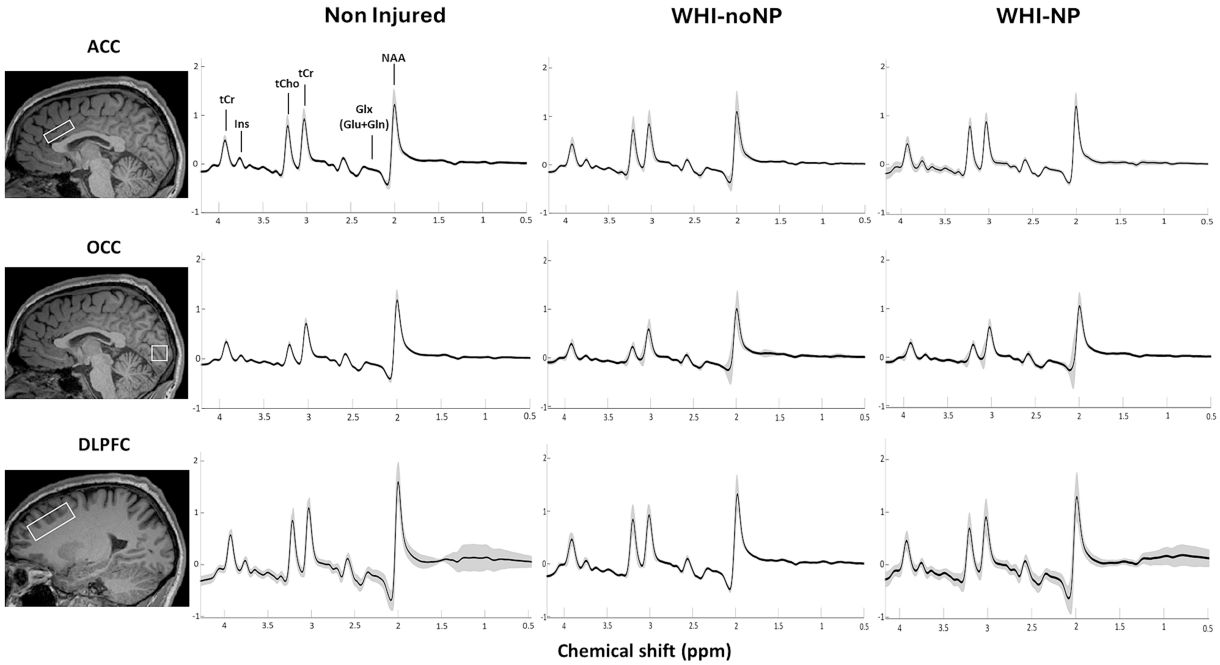

FIGURE 1
An example of a representative MR spectra, illustrating voxel mask placement for the anterior cingulate cortex **(A)**, occipital cortex **(B)**, and left dorsolateral prefrontal cortex **(C)**. Typical MRS spectra from the anterior cingulate cortex of a healthy participant **(D)**.

TABLE 1 Demographic and clinical characteristics of healthy non-injured individuals, participants with whiplash-associated disorders without neuropathic pain (WAD-noNP), and participants with whiplash-associated disorders with neuropathic pain components (WAD-NP).

	Non-injured ($n = 29$)	WAD ($n = 29$)	WAD-noNP ($n = 15$)	WAD-NP ($n = 14$)
Age	25.0 (21.8–40.8)	39.0 (30.0–45.8)**	40.0 (33.5–48.8)	38.5 (29.0–43.0)
Sex, n (%) female	16.0 (55.2%)	20 (69.0%)	8 (53.3%)	12 (85.7%)
% WAD IIa	0	3 (10.3%)	3 (20%)	0##
% WAD IIb	0	14 (48.3%)	10 (66.7%)	4 (28.6%)##
% WAD III	0	12 (41.4%)	2 (13.3%)	10 (71.4%)##
Evaluation time since WHI (days)	0	100 (89–108)	102 (95–108)	98 (87–117)
MRS time since WHI (days)	0	100.6 ± 32.7	94.1 ± 27.1	108.1 ± 37.9
7-day pain intensity (NRS:0–10)	0	4 (1–6)	1 (0–4)	6 (4–6) †
DN4 (0–10)	0	3.0 (0.8–6.0)	1.0 (0.0–3.0)	6.0 (4.0–7.0) ††
Pain interference (BPI REM)	0	1.5 (0.0–4.8)	0.0 (0.0–0.3)	4.7 (2.9–7.3) ††
Pain interference (BPI WAW)	0	2.7 (0.0–5.7)	0.0 (0.0–1.3)	5.7 (3.5–7.3) ††
Pain interference (total BPI)	0	2.8 (0.2–5.6)	0.3 (0.0–1.2)	5.2 (4.1–7.3) ††

Data are shown as mean (± SD) or median scores (25th–75th percentiles).
**(Non-injured vs. WHI, *t*-test, $p < 0.01$).
##(WAD-noNP vs. WAD-NP, chi-square, $p < 0.01$).
†(WAD-noNP vs. WAD-NP, Mann–Whitney, $p < 0.01$).
††(WAD-noNP vs. WAD-NP, Mann–Whitney, $p < 0.001$).
DN4, Douleur Neuropathique 4; NRS, Numeric Rating Scale; BPI, Brief Pain Inventory: REM (Relation with others, Enjoyment of Life, Mood), WAW (Walking, General Activity, Working); WAD-noNP, whiplash-associated disorders without neuropathic pain; WAD-NP, whiplash-associated disorders with neuropathic pain.

were included in the basis files. The basis set contained 18 basis spectra for edit-off, out of which 7 were reported: total creatine (Cr), total n-acetyl-aspartate (NAA), inositol (Ins), total choline (Cho), glutamate and glutamine (Glx), glutamate (Glu), and gamma-aminobutyric acid (GABA+) and normalised to total creatine (tCr). Importantly, no difference in creatine levels was identified between groups, and therefore, metabolite ratio values were calculated using tCr. In this study, glutamate was not highly correlated with glutamine (Spearman's correlation: 0.43) in line with other sequences using 3 T scanners (58). Quality control measures as recommended by the MRSinMRS consensus group are shown in Supplementary Table S2 and are presented as signal-to-noise ratio (SNR), line width (LW), full-width-half maximum (FWHW), and Cramér–Rao Lower Bound (CRLB) for each metabolite.

2.7 Statistical analyses

Statistical analysis was performed with a commercial software package (SigmaPlot 11.0 for Windows, Systat Software, Inc., Germany). Metabolite data were expressed either as mean ± standard deviation or as median values with 25th–75th interquartile percentiles, according to the Shapiro–Wilk normality test. Intergroup differences in metabolite concentrations were detected either with the Student's *t*-test or Mann–Whitney test for comparisons between the healthy and WHI groups or with the one-way analysis of variance (ANOVA) or Kruskal–Wallis test for comparisons between the three groups: healthy, WAD without NP (WAD-noNP), and WAD with NP (WAD-NP). Bonferroni tests were performed with the Holm–Sidak or Dunn's method. Intergroup clinical data were compared using the Student's *t*-test or Mann–Whitney test. Differences and the impact of age and sex on significant differences in metabolite concentrations were assessed with an analysis of covariance (ANCOVA) using a different commercial package (JASP, version 0.18.1.0). The possible impact of age-related differences on metabolite concentrations in the healthy younger non-injured group was also controlled by performing analysis with the general WAD group and also specifically by comparing differences between the WAD-noNP and WAD-NP groups.

To reduce the number of multiple comparisons between brain MRS metabolites within the ACC, DLPFC, and OCC with the DN4 screening score, a best-fit analysis was first performed for each metabolite (SigmaPlot 11.0). A forward stepwise multiple linear regression analysis was performed to identify the best predictive model for both the metabolite concentrations for total Cr, total NAA, Ins, total Cho, Glx, Glu, and GABA and also for metabolite concentrations normalised to total Cr (27). In addition, the statistical power was reported for each predictive model.

Spearman's correlation coefficient was calculated to assess the relationship of the metabolite concentrations that best predicted NP components as measured with the DN4 screening questionnaire.

3 Results

3.1 Demographic and clinical characteristics

Demographic and clinical data of recruited participants are presented in Table 1. No significant differences based on age or sex were seen in non-injured participants compared with those with WHI, or with the WAD-noNP-NP and WAD-NP. Furthermore, no differences were revealed between groups with reference to the time of clinical or MRS evaluation.

Significant differences were revealed in the clinical characteristics for the number of participants diagnosed with WHI with WAD IIa, IIb, and III ($p < 0.001$). Specifically, participants reported NP components with either a WAD IIb (29%) or III (72%) grade. Finally,

TABLE 2 Occipital cortex (OCC) metabolite concentration (mM) and metabolite ratios normalised to total creatine (tCr) in healthy non-injured individuals, participants with whiplash-associated disorders without neuropathic pain (WAD-noNP), and participants with whiplash-associated disorders with neuropathic pain components (WAD-NP).

	Non-injured ($n = 29$)	WAD ($n = 29$)	WAD-noNP ($n = 15$)	WAD-NP ($n = 14$)
tCr	5.60 ± 0.48	5.70 ± 0.53	5.64 ± 0.55	5.77 ± 0.53
tCho	1.02 ± 0.11	1.08 ± 0.16	1.06 ± 0.16	1.11 ± 0.16
NAA	10.82 ± 1.08	10.91 ± 1.3	10.77 ± 1.41	11.05 ± 1.20
Glx	7.04 (6.07–8.06)	6.88 (6.05–7.72)	6.10 ± 1.96	7.24 ± 1.41
Ins	6.45 (5.98–7.02)	7.06 (6,33–7,31)	6.94 (86.30–7.23)	7.00 (6.08–7.35)
GABA	1.34 (0.98–1.48)	1.31 (1.14–1.66) ¶ ¶	1.30 (1.09–1.51) ¶	1.60 (1.17–1.78)
Glu	2.97 (2.59–3.67)	2.74 (1.77–3.70) ¶	2.70 ± 1.39 ¶	2.68 ± 1.19
tCho/tCr	0.18 ± 0.02	0.19 ± 0.02	0.19 ± 0.02	0.19 ± 0.017
NAA/Cr	1.93 ± 0.11	1.91 ± 0.14	1.91 ± 0.15	1.92 ± 0.15
Glx/tCr	1.21 (1.12–1.39)	1.23 (1.06–1.28)	1.16 (0.97–1.28)	1.24 (1.15–1.37)
Ins/tCr	1.18 ± 0.14	1.22 ± 0.19	1.25 ± 0.22	1.19 ± 0.15
GABA/tCr	0.23 (0.19–0.26)	0.23 (0.2–0.28) ¶ ¶	0.23 (0.19–0.27) ¶	0.26 (0.20–0.32) ¶
Glu/tCr	0.54 ± 0.15	0.48 ± 0.18 ¶ ¶	0.51 ± 0.18 ¶ ¶	0.46 ± 0.19

Cr, Total creatine; NAA, total n-acetyl-aspartate; Ins, Inositol; tCho, total choline; Glx, glutamate and glutamine; Glu, glutamate; GABA+, gamma-aminobutyric acid. tCho is calculated as the sum of phosphocholine (pCho) and glycerophosphocholine (GPC).
*(non-injured vs. WAD, *t*-test, $p < 0.05$).
¶(1 subject with unanalysable metabolite data).
¶¶(2 subjects with unanalysable metabolite data).
Data are shown as mean (± SD) or median scores (25th–75th percentiles).

higher scores for 7-day pain intensity and interference were measured with the total BPI or subscores when compared between the WAD-noNP and WAD-NP groups ($p < 0.001$) (Table 1).

3.2 Metabolite concentrations within the OCC, ACC, and DLPFC

No difference in concentration (mM) or normalised metabolite levels were revealed in the OCC compared to the groups (Table 2). In contrast, concentration (mM) and normalised glutamate levels within the ACC were higher in the WAD-NP group compared to the WAD-noNP group. The normalised Glu/tCr concentration was higher in the healthy compared to the general WAD group ($p < 0.01$) and WAD-noNP group within the ACC (Table 3) ($p < 0.05$), but not in the DLPFC (Table 4) or OCC (Table 2). Furthermore, the tCho/tCr metabolite ratio within the DLPFC was higher in the WAD-noNP than in the healthy group (Table 4) ($p < 0.025$). Neither sex nor age or normalised metabolite concentrations affected concentration (mM) related to WAD-NP components when compared to the WAD-noNP group..

Regarding the left DLPFC, lower concentration (mM) and normalised tCho were found in the WAD-NP group than in the WAD-noNP group. Finally, a reduction in concentration (mM) Ins metabolite levels in DLPFC is shown in the WAD-NP group compared to the WAD-noNP group.

3.3 Best fit and forward stepwise regression analysis of MRS metabolites

The best fit and multiple linear regression between metabolite concentrations within the OCC, ACC, and DLPFC with the DN4 screening scores is shown in Table 5. Forward stepwise regression revealed that chronic normalised glutamate concentrations predicted chronic WAD-NP components ($r^2 = 0.26$, $p < 0.01$, alpha = 0.81) as shown in Figure 2A (rho = 0.54, $p = 0.003$). In the left DLPFC, both concentration (mM) and normalised tCho and NAA metabolite concentrations predicted chronic WAD-NP components ($r^2 = 0.62$, with significance ranging between $p < 0.05$ and $p < 0.001$, alpha = 0.98) as shown in Figure 2B (rho = −0.66, $p = 0.004$), Figure 2C (rho = −0.62, $p = 0.01$), and Figure 2D (rho = 0.25, $p = 0.336$).

4 Discussion

This is the first study to show significant differences in metabolite concentrations within pain-processing cortical areas, such as the ACC and DLPFC, in participants with chronic whiplash injury and WAD neuropathic pain components when compared to individuals without WAD-NP components. Importantly, the adoption of the latest MRSinMRS recommendations for metabolite analysis, including calibration with a simulated basis set into the analysis routine, and rigorous signal preprocessing including quality control, may have contributed to improved metabolite detection and quantification of metabolite differences during chronic WAD-NP. Indeed, elevated glutamate concentrations within the ACC predicted chronic WAD-NP components, while higher NAA and lower tCho metabolite levels within the DLPFC suggest a role for increased neuronal–glial signalling and neuronal membrane dysfunction with central chronic pain mechanisms. Radiological evidence for biochemical differences in affective pain-processing areas provides further evidence of the involvement of definite NP components in chronic WAD.

Although this study was performed on a small cohort of individuals reporting chronic WAD pain with neuropathic

TABLE 3 Anterior cingulate cortex (ACC) metabolite concentration (mM) and metabolite ratios normalised to total creatine (tCr) in healthy non-injured individuals, participants with whiplash-associated disorders without neuropathic pain (WAD-noNP), and participants with whiplash-associated disorders with neuropathic pain components (WAD-NP).

	Non-injured (*n* = 29)	WAD (*n* = 29)	WAD-noNP (*n* = 15)	WAD-NP (*n* = 14)
tCr	6.58 (5.77–6.83)	6.54 (5.96–7.14)	6.54 (5.92–7.19)	6.57 (5.98–6.95)
tCho	2.16 (1.93–2.33)	2.19 (1.84–2.52)	2.32 (1.87–2.54)	2.17 (1.85–2.38)
NAA	10.26 (8.35–11.09)	10.44 (8.51–11.01)	10.44 (8.48–11.13)	10.31 (8.73–10.68)
Glx	7.64 ± 1.20	7.53 ± 1.31	7.44 ± 1.28	7.63 ± 1.38
Ins	7.15 ± 1.31	7.56 ± 1.44	7.59 ± 1.58	7.53 ± 1.34
GABA	1.12 (1.05–1.35)	1.26 (1–1.50)	1.19 ± 0.32	1.29 ± 0.32
Glu	5.15 ± 0.97	4.62 ± 1.19	4.21 ± 1.33**#1**	5.05 ± 0.85◊**#2**
tCho/tCr	0.34 (0.32–0.36)	0.35 (0.32–0.39)	0.34 (0.31–0.39)	0.34 (0.32–0.37)
NAA/Cr	1.58 ± 0.11	1.52 ± 0.12	1.51 ± 0.13	1.54 ± 0.10
Glx/tCr	1.20 ± 0.09	1.17 ± 0.12	1.14 ± 0.11	1.21 ± 0.13
Ins/tCr	1.12 (1.04–1.22)	1.14 (1.04–1.32)	1.14 (1.01–1.39)	1.15 (1.05–1.30)
GABA/tCr	0.19 ± 0.04	0.19 ± 0.04	0.18 ± 0.05	0.21 ± 0.04
Glu/tCr	0.82 (0.75–0.88)	0.76 (0.67–0.79)††	0.67 (0.58–0.76)**#3**	0.78 (0.76–0.85) ◘◘◘**#4**

Cr, Total creatine; NAA, total n-acetyl-aspartate; Ins, Inositol; tCho, total choline; Glx, glutamate and glutamine; Glu, glutamate; GABA+, gamma-aminobutyric acid. tCho is calculated as the sum of phosphocholine (pCho) and glycerophosphocholine (GPC).
Data are shown as mean (± SD) or median scores (25th –75th percentiles).
††(non-injured vs. WHI, Mann–Whitney, $p < 0.01$).
◊(one-way ANOVA, $p < 0.05$).
#1(non-injured vs. WAD-noNP, Holm–Sidak $p < 0.05$).
#2(WAD-noNP vs. WAD-NP, Holm–Sidak $p < 0.05$).
◘◘◘(Kruskal–Wallis, $p < 0.001$).
#3(non-injured vs. WAD-noNP, Dunn's method $p < 0.05$).
#4(WAD-NP vs. WAD-noNP, Dunn's method $p < 0.05$).

TABLE 4 Left dorsolateral prefrontal cortex (DLPFC) metabolite concentration (mM) and metabolite ratios normalised to total creatine (tCr) in healthy non-injured individuals, participants with whiplash-associated disorders without neuropathic pain (WAD-noNP), and participants with whiplash-associated disorders with neuropathic pain components (WAD-NP).

	Non-injured (*n* = 13)	WAD (*n* = 17)	WAD-noNP (*n* = 8)	WAD-NP (*n* = 9)
tCr	7.65 ± 0.57	7.52 ± 0.89	7.87 ± 0.71	7.21 ± 0.96
tCho	2.48 ± 0.40	2.70 ± 0.60	3.07 ± 0.48**#1**	2.37 ± 0.51**#2**
NAA	13.43 ± 1.97	12.67 ± 1.69	12.91 ± 1.38	12.44 ± 1.99
Glx	9.75 ± 1.31	10.11 ± 1.41	10.22 ± 1.75	10.01 ± 1.14
Ins	11.18 ± 1.08	11.35 ± 2.21	12.54 (12.09–13.82)	10.98 (9.29–11.18)◘◘**#3**
GABA	1.39 ± 0.41	1.23 ± 0.38	1.22 ± 0.34	1.24 ± 0.44
Glu	5.72 ± 0.72	5.07 ± 1.48¶	5.05 ± 1.80	5.08 ± 1.19 ¶
tCho/tCr	0.32 ± 0.05	0.36 ± 0.055	0.39 ± 0.04**#4**	0.33 ± 0.05◊◊**#5**
NAA/Cr	1.75 ± 0.19	1.69 ± 0.16	1.65 ± 0.14	1.73 ± 0.17
Glx/tCr	1.28 ± 0.14	1.35 ± 0.16	1.30 ± 0.19	1.40 ± 0.12
Ins/tCr	1.46 ± 0.13	1.50 ± 0.19	1.58 ± 0.25	1.43 ± 0.07
GABA/tCr	0.18 ± 0.05	0.17 ± 0.06	0.16 ± 0.05	0.17 ± 0.07
Glu/tCr	0.75 ± 0.09	0.68 ± 0.18¶	0.63 (0.50–0.69)	0.77 (0.70–0.82) ◘ ¶

Cr, Total creatine; NAA, total n-acetyl-aspartate; Ins, Inositol; tCho, total choline; Glx, glutamate and glutamine; Glu, glutamate; GABA+, gamma-aminobutyric acid. tCho is calculated as the sum of phosphocholine (pCho) and glycerophosphocholine (GPC).
Data are shown as mean (± SD) or median scores (25th–75th percentiles).
¶(1 subject with unanalysable metabolite data).
◊◊(one-way ANOVA, $p < 0.01$).
#1(non-injured vs. WAD-noNP, Holm–Sidak $p < 0.05$).
#2(WAD-noNP vs. WAD-NP, Holm–Sidak $p < 0.025$).
◘(Kruskal–Wallis, $p = 0.06$).
◘◘(Kruskal–Wallis, $p < 0.01$).
#3(WAD-NP vs. WAD-noNP, Dunn's method $p < 0.05$).
#4(non-injured vs. WAD-noNP, Holm–Sidak $p < 0.025$).
#5(WAD-noNP vs. WAD-NP, Holm–Sidak $p < 0.05$).

TABLE 5 Best-fit factor and forward multiple regression analysis for occipital cortex (OCC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC) MRS metabolite concentration (mM) and ratio normalised to tCr with DN4 scores for participants with chronic WAD with NP components.

Concentration (mM) metabolite	OCCIP	ACC	DLPFC
tCr	E.	**−1.45 ± 0.69***	E.
Glx	**1.23 ± 0.48***	E.	**0.9 ± 0.31***
NAA	−0.65 ± 0.56	E.	**0.76 ± 0.04***
tCho	E.	E.	**−4.08 ± 0.89*****
Ins	−0.35 ± 0.44	0.18 ± 0.35	**−0.55 ± 0.03***
GABA	E.	2.48 ± 1.52	−1.02 ± 0.99
Glu	−0.68 ± 0.48	**1.29 ± 0.44****	E.
Best subset regression r^2	0.31	0.34	0.83
Forward stepwise r^2	E.	Glu (0.91 ± 0.38) **r^2 = 0.18**	NAA (0.56 ± 0.34) tCho (−1.04 ± 0.95) **r^2 = 0.62**
Power α	E.	0.63	**0.98**
Metabolite Normalised Ratio (tCr)	**OCCIP**	**ACC**	**DLPFC**
Glx/tCr	**7.34 ± 2.96***	−0.63 ± 4.23	**6.44 ± 2.34***
NAA/Cr	−3.99 ± 3.90	0.63 ± 3.78	3.09 ± 2.60
tCho/tCr	E.	E.	**−30.19 ± 6.59*****
Ins/tCr	E.	E.	**−5.26 ± 2.14***
GABA/tCr	E.	16.74 ± 10.98	E.
Glu/tCr	−4.56 ± 2.84	**8.55 ± 3.29***	E.
Best subset regression r^2	E.	0.33	0.81
Forward stepwise r^2	E.	Glu/tCr (8.62 ± 2.83) **r^2 = 0.26**	tCho/tCr (−34.82 ± 8.30) NAA/Cr (7.36 ± 2.88) **r^2 = 0.62**
Power α	E.	**0.81**	**0.98**

Cr, Total creatine; NAA, total n-acetyl-aspartate; Ins, Inositol; tCho, total choline; Glx, glutamate and glutamine; Glu, glutamate; GABA+, gamma-aminobutyric acid. tCho is calculated as the sum of phosphocholine (pCho) and glycerophosphocholine (GPC). Data are shown as mean (± SE). E. Excluded.
*($p < 0.05$), ** ($p < 0.001$), *** ($p < 0.001$). Significant results presented in bold.

components, statistically powered predictive correlations were attained between the glutamate/tCr ratio in the ACC (α = 0.81) and the tCho/tCr and NAA/tCR ratios in DLPFC with WAD-NP components (DN4, α = 0.98). Furthermore, metabolites within the DLPFC region revealed a higher regression value with NP components in chronic WAD ($r^2 = 0.62$ [compared to an r^2 of 0.26 within the ACC]). Importantly stepwise regression was not able to detect predictive relationships between metabolite levels and WAD-NP components within the occipital cortex, which was included in this study as a putative control ROI.

4.1 Neuropathic pain components associated with chronic WAD

Approximately 34% (25–75%) of patients present NP characteristics following WHI, characterised by sensory dysfunction and nerve mechanosensitivity (59). Pain associated with WAD has often been diagnosed as musculoskeletal pain in the absence of clear evidence of nerve or brain lesions tested using neurophysiological or radiological techniques; pain and sensory disturbances in a neuroanatomically defined area consistent with a specific nerve lesion have not been forthcoming for WAD (45). However, an early study of NP symptoms and signs in patients with acute WHI (8) and, more recently, small fibre structural and functional deficits in chronic WAD have been demonstrated (9).

In this study, 48% of the chronic WHI cohort presented NP symptoms and signs as measured with the DN4 questionnaire. Compared with the WAD-noNP group, individuals with chronic WAD-NP were characterised by a higher 7-day pain intensity (NRS) and pain interference scores (BPI). For those subjects diagnosed with WAD grade II and III scores, NP symptoms and signs were detected, suggesting that NP components were associated with or without presumed central or peripheral nerve injury. The difficulty in diagnosing and differentiating musculoskeletal and NP components may lead to poor treatment, which could be improved with the extensive use of NP screening tools and the detection of pain types (39, 60). Accurate small nerve fibre examination (9) and radiological evidence of either structural or biochemical differences within pain-processing areas of the brain, especially those related to affective pain, may help to support the clinical diagnosis of chronic NP with sensory descriptors and changes during chronic WHI.

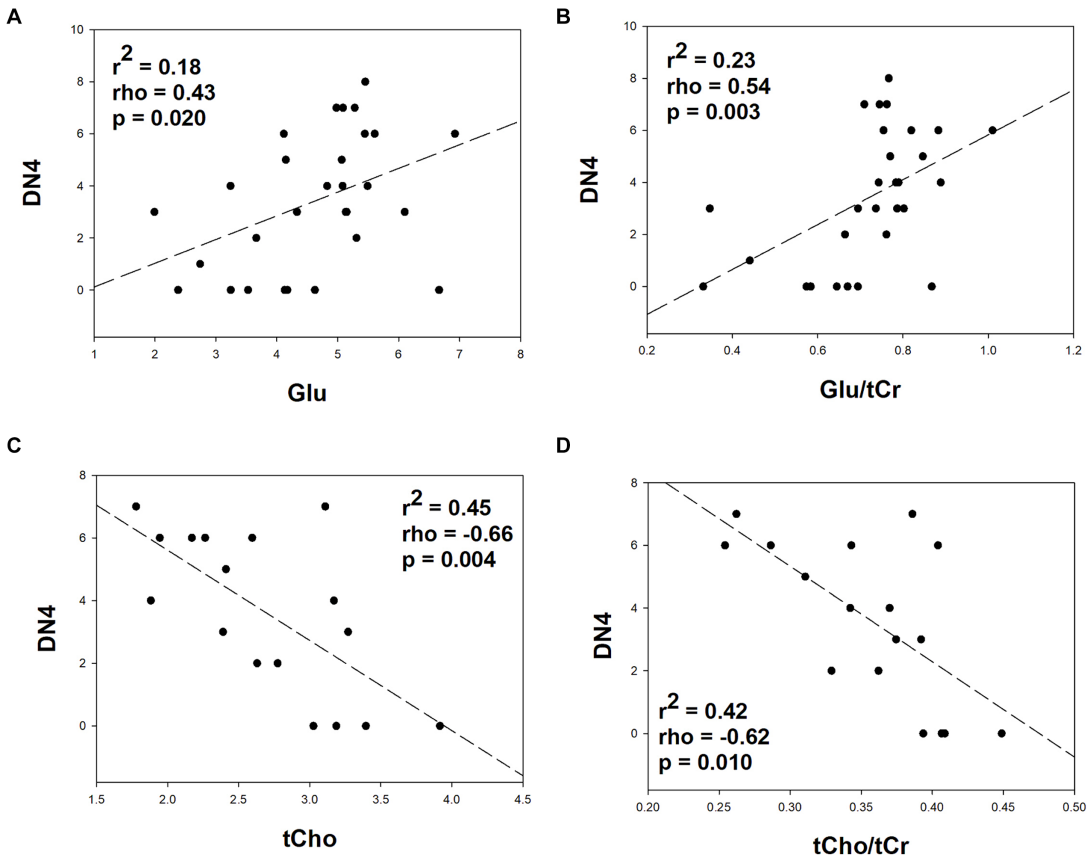

FIGURE 2
Relationship between metabolite concentrations quantified using brain MRS within the anterior cingulate (**A,B**; *n* = 29) and left prefrontal dorsolateral cortex (**C,D**; *n* = 17) and neuropathic pain components as screened with the "douleur neuropathique 4" (DN4) screening tool in participants with chronic whiplash injury. The regression coefficient, Spearman correlation, and statistical significance of the correlation are included in each graph. To reduce type II error Spearman correlations were calculated only from the best predictive models of metabolite measures for chronic WAD-NP components.

4.2 Current application of MRI techniques for chronic pain and consensus-driven MRS analysis

Proton magnetic resonance spectroscopy (^{1}H MRS) imaging of pain-processing areas permits a mechanistic approach to detect site specific biochemical changes in neuronal and glial cell dysfunction and can be used to demonstrate the therapeutic effects of analgesic treatments (22–24) and non-invasive neuromodulation of the cortex (25, 26). However, ^{1}H MRS imaging is only one of several non-invasive techniques that enable quantification of structural, functional, or biochemical alterations in brain function for chronic pain research (61) that collectively can provide an essential insight into pathophysiological mechanisms and therapeutic targets. These techniques have proven highly effective in revealing alterations in brain regions implicated in pain modulation (62, 63) and emotional processing (64, 65). However, challenges persist regarding the application of MRI techniques in pain research, such as issues related to protocol standardisation and variability in imaging results across studies. Future directions for researchers may involve refining imaging protocols to enhance reproducibility (66), adoption of multimodal imaging techniques, and developing machine learning algorithms for more precise analysis of MRI data (67–69).

The technical challenges associated with the ^{1}H MRS imaging and metabolite analysis (30, 31, 70) may explain the failure to detect subtle differences in metabolite concentrations related to chronic WHI pain (27). Analysis methods available on scanner software are usually inferior to demonstrating differences in metabolite concentrations with MRS techniques, and therefore, expert consensus groups recommend the use of software that allows pre-processing, such as phase and frequency correction, quality control, tissue segmentation, and final metabolite quantification using modelling algorithms (30). In this study, the use of the semi-adiabatic localisation by adiabatic selective refocusing (semi-LASER) sequence (30), single-voxel spectroscopy imaging of specific anatomical regions (30, 31), and the development and implementation of a simulated basis set into the analysis routine (30) were implemented into the analysis routine. Furthermore, a binary mask of voxel locations was co-registered with the T1-weighted images, and this mask was applied using SPM12 scripts to determine total tissue (grey and white matter) and cerebrospinal fluid fractions in each voxel (26). A checklist for full reporting of MRS parameters in line with the recommendation of the MRSinMRS consensus group (66) was followed, and metabolite

concentrations were presented as concentration (mM) values and ratios normalised to total creatine levels (71). Finally, the possible contribution of demographic cofactors, such as sex and age, should also addressed with ANCOVA (72, 73). In the present study, these techniques have ensured high-quality analysis of metabolite concentration levels and detection of group differences in the ACC and DLPFC, but not the OCC, for metabolites that predict WAD-NP components.

4.3 Higher glutamate concentration in ACC predicts chronic WAD-NP components

The anterior cingulate cortex (ACC) plays a leading role in chronic pain, specifically in the modulation of affective and mood components (32, 33). This is supported by synaptic, molecular structural changes in the ACC, which contribute to chronic pain states (74–76). The ACC is also implicated in the cognitive impairment in chronic pain patients, potentially mediating the impact of pain-related distress on cognitive functions (32, 77). Thus, the ACC is a potential target for neuromodulation and clinical pain management (24, 25, 78).

In this study, MRS revealed elevated concentration (mM) and normalised glutamate concentrations in the group with WAD-NP components and a significant predictive relationship between normalised glutamate ratios with the DN4 NP scores. Glutamate as the main excitatory neurotransmitter has a leading role in nociception and central sensitisation, which is associated with chronic pain (79). Glx (glutamate plus glutamine) levels pooled across pain-related brain regions have been positively associated with pain sensitivity (15), while tonic noxious stimulation leads to increased concentrations of glutamate and Glx at the onset of pain (80). Higher glutamate levels within the ACC have been shown in individuals with chronic low back pain (81, 82), while Glx levels have also been linked to psychological state and depression (82). Furthermore, treatment with transcranial direct current stimulation or morphine decreases Glx levels in the ACC (23–25), suggesting a potential mechanism for its analgesic effect. Future studies should assess the relationship between normalised ACC glutamate metabolite concentrations with pain intensity and affective measures in people with chronic WAD-NP components.

4.4 Lower total choline levels and higher n-acetyl-aspartate DLPFC metabolite concentrations predict the presence of chronic WAD-NP components

The dorsolateral prefrontal cortex (DLPFC) undergoes a functional and structural reorganisation in chronic pain conditions (83) and plays a crucial role in the modulation of pain perception and processing. Thus, the DLPFC exerts active control on pain perception by modulating pain signals in the brain (34). In fact, Ong et al. (84) and Loggia et al. (85) highlight the involvement of the DLPFC in pain modulation, emphasising its role in chronic pain and negative cognition-induced hyperalgesia. These findings highlight the importance of the DLPFC in chronic pain and its potential as a target for therapeutic interventions.

In this study, lower total choline (tCho) concentrations predicted WAD-NP components during chronic pain. Phosphocholine and glycerophosphoryl choline are key components in cell membrane synthesis and a marker of cellular turnover (86) and are associated with glia cells within the brain (87). Neuropathic pain can lead to changes in choline levels following head trauma within pain-processing centres (13, 19). Moreover, neuropathic pain has been associated with neuroinflammation, characterised by elevated choline-containing compounds, such as phosphocholine, found in higher concentrations in glial cells than neurons (10). However, only one study has shown reduced chronic choline levels in cases of human immunodeficiency virus infection, with initially elevated levels of choline levels which then decreased significantly at a later stage (88). Although the exact pathophysiological mechanism that implicates reduced choline levels with chronic pain is unknown, it is of interest that cortical targeting of central cholinomimetics has been suggested as an effective therapy for neuropathic pain (89). Indeed, choline supplementation can have beneficial effects on brain health, including reducing inflammation and cognitive deficits in an experimental model of Alzheimer's disease (90).

Even though N-acetyl-aspartate is a metabolite related to neuronal density activity or cell death (91), higher concentrations of NAA have been recently identified in myelin and oligodendrocytes compared with neurons (92). Although previous studies of lower NAA levels in the DLPFC have been related to chronic back pain (12, 93), higher NAA levels have been associated in other pain-processing areas with chronic NP severity, post-traumatic stress disorder, and post-concussive symptoms in individuals with traumatic brain injury (19). Taken together, lower choline and higher NAA levels may be related to pathophysiological mechanisms associated with neuroinflammation during chronic WHI pain and may represent robust biomarkers of chronic WAD pain with neuropathic components.

4.5 Study limitations

This study was not conducted on age- or gender-matched individuals within each group. Importantly, analysis of covariance demonstrated that neither sex nor age or normalised metabolite concentrations affected concentration (mM) related to WAD-NP components when compared to the WAD-noNP group. However, in this study, higher glutamate concentrations were found in the healthy non-injured group than in the WHI-noNP group. In line with the demographic data presented in Table 1, which shows that the median age of the WAD-NP was 14 years lower than the general WHI group, glutamate levels are known to be higher in younger subjects (94). When metabolite concentrations in the WHI-NP group were specifically compared to the WHI-noNP control group, ROI-specific changes in glutamate were seen in both the ACC and DLPFC. Importantly, no differences in glutamate ratio concentration were observed between the non-injured and WHI-noNP control groups (Table 4). Finally, caution should also be made with the interpretation of tCho in spectroscopy studies, as higher tCho metabolite concentrations have been observed in older healthy subjects (95), which may explain the higher levels of this metabolite identified in the DLPFC for the WHI-noNP control group (Table 4).

Reliance on stepwise regression analysis to identify target metabolites associated with WAD-NP components may be influenced by several statistical problems with this test, including overfitting of data, biased estimates, and inflated type I errors (96). As such, significant best-fit metabolites should also be considered as predictors for NP components in chronic WAD components, including GABA and Ins (10, 20, 27, 97). The best-fit analysis performed in this study demonstrated that lower Ins concentrations in DLPFC are a predictor of chronic NP components, although previous studies have revealed a relationship between higher Ins levels and chronic pain with other pathologies (19, 82). The relationship between Ins metabolite levels and chronic pain may reflect differences between different pain pathologies (10, 13). In future studies, parallel adoption of multiple regression and machine learning analysis techniques may provide a better interpretation of key metabolite levels in the development of chronic pain (67, 68).

Although no metabolite predictors of chronic WAD pain were identified in the OCC, the inclusion of control areas should be more closely examined in longitudinal studies where the contribution of metabolite changes to the development of chronic pain can be assessed during acute WAD. Indeed, chronic WAD dysfunction of the visual system is associated with functional impairment in occipital cortical areas sensitive to coherent motion (98) while EEG changes in OCC have been associated with motor-evoked jaw pain (99).

Finally, total creatine concentrations in MRS studies have been used to standardise metabolite levels in the brain. In this study, no difference in creatine levels was identified between groups, although lower concentrations (mM) of creatine levels within the ACC were associated with NP components in the best-fit analysis. It is important to understand therefore that these basal Cr levels, which are expressed predominantly in glia, may also change during neuroinflammation (10, 100) or with age (73). These findings suggest that caution should be made with the normalisation of metabolite levels using ratio measures (27).

5 Conclusion

The results of this study show that elevated glutamate concentrations within the ACC predict chronic WAD-NP components, while higher NAA and lower total choline (tCho) metabolite levels within the DLPFC suggest a role for increased neuronal–glial signalling and cell membrane dysfunction with central chronic pain mechanisms. No chronic differences were seen in the occipital cortex, which supports the role of altered metabolite concentrations within the affective pain-processing areas such as the ACC and DLPFC. Detection of metabolite signals that reflect pathophysiological mechanisms of glutamatergic, neuroinflammatory, and cell signalling dysfunction could lead to a better understanding of the development of pathophysiological mechanisms of chronic pain that lead to high-impact chronic NP components of chronic WAD and future therapeutic targets for the neuromodulation of chronic WHI pain.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Toledo Hospital Complex Clinical Research Ethics Committee (Nº 2559/674; 17/02/2021). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

IP-F: Writing – original draft, Writing – review & editing. MR-L: Writing – original draft, Writing – review & editing. DD: Writing – original draft, Writing – review & editing. LG: Writing – original draft, Writing – review & editing. MT-L: Writing – original draft, Writing – review & editing. FG-G: Writing – original draft, Writing – review & editing. MV: Writing – original draft, Writing – review & editing. II: Writing – original draft, Writing – review & editing. HB: Writing – original draft, Writing – review & editing. JT: Writing – original draft, Writing – review & editing. AB-M: Writing – original draft, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Grant PID2020-119948RB-I00 funded by MCIN/AEI/10.13039/501100011033, ADESLAS-Mutua Madrileña (2020), Fundación Koplowitz, and by "ERDF A way of making Europe". II was funded by a Royal Society Dorothy Hodgkin Research Fellowship and a Medical Research Council grant (MR/V034723/1). The MRS package (MEGA-semi-LASER) was developed by Edward J. Auerbach and Małgorzata Marjańska and provided by the University of Minnesota under a C2P agreement. IP-F was funded by the Investigo Programme sponsored by the European Union, NextGenerationEU, and the Ministry of Work and Social Economy in Spain.

Acknowledgments

We acknowledge the expert help of Małgorzata Marjańska of the Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota, and William Clarke of the Wellcome Centre for Integrative Neuroimaging, FMRIB, Nuffield Department of Clinical Neurosciences, and MRC Brain Network Dynamics Unit, University of Oxford. Special thanks to our Radiology Team Technicians and Clinicians: María del Mar Rodrigo-Nieto, Celia Gómez-Domínguez, Antonio Martínez-Porcel, Manuel Cobo-Civantos, Ángel Torrado-Carvajal, Miguel Rodríguez-Cola, and Irena Jiménez-Velasco.

Conflict of interest

MV was employed by company Siemens Healthineers.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer DM declared a shared affiliation with the author AB-M to the handling editor at the time of review.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1404939/full#supplementary-material

References

1. Kasch H, Qerama E, Kongsted A, Bach FW, Bendix T, Jensen TS. Deep muscle pain, tender points and recovery in acute whiplash patients: a 1-year follow-up study. *Pain*. (2008) 140:65–73. doi: 10.1016/j.pain.2008.07.008

2. Daenen L, Nijs J, Roussel N, Wouters K, Van Loo M, Cras P. Dysfunctional pain inhibition in patients with chronic whiplash-associated disorders: an experimental study. *Clin Rheumatol*. (2013) 32:23–31. doi: 10.1007/s10067-012-2085-2

3. Vallez Garcia D, Doorduin J, Willemsen AT, Dierckx RA, Otte A. Altered regional cerebral blood flow in chronic whiplash associated disorders. *EBioMedicine*. (2016) 10:249–57. doi: 10.1016/j.ebiom.2016.07.008

4. Seroussi R, Singh V, Fry A. Chronic whiplash pain. *Phys Med Rehabil Clin N Am*. (2015) 26:359–73. doi: 10.1016/j.pmr.2015.01.003

5. Van Oosterwijck J, Nijs J, Meeus M, Paul L. Evidence for central sensitization in chronic whiplash: a systematic literature review. *Eur J Pain*. (2013) 17:299–312. doi: 10.1002/j.1532-2149.2012.00193.x

6. Bellosta-Lopez P, Domenech-Garcia V, Ortiz-Lucas M, Lluch-Girbes E, Herrero P, Sterling M, et al. Longitudinal changes and associations between quantitative sensory testing and psychological factors in whiplash-associated disorders: a systematic review and Meta-analyses-based data synthesis. *J Pain*. (2024) 25:12–30. doi: 10.1016/j.jpain.2023.07.021

7. Davis CG. Mechanisms of chronic pain from whiplash injury. *J Forensic Leg Med*. (2013) 20:74–85. doi: 10.1016/j.jflm.2012.05.004

8. Sterling M, Pedler A. A neuropathic pain component is common in acute whiplash and associated with a more complex clinical presentation. *Man Ther*. (2009) 14:173–9. doi: 10.1016/j.math.2008.01.009

9. Farrell SF, Sterling M, Irving-Rodgers H, Schmid AB. Small fibre pathology in chronic whiplash-associated disorder: a cross-sectional study. *Eur J Pain*. (2020) 24:1045–57. doi: 10.1002/ejp.1549

10. Chang L, Munsaka SM, Kraft-Terry S, Ernst T. Magnetic resonance spectroscopy to assess Neuroinflammation and neuropathic pain. *J Neuroimmune Pharmacol*. (2013) 8:576–93. doi: 10.1007/s11481-013-9460-x

11. Schmidt-Wilcke T. Neuroimaging of chronic pain. *Best Pract Res Clin Rheumatol*. (2015) 29:29–41. doi: 10.1016/j.berh.2015.04.030

12. Zhao X, Xu M, Jorgenson K, Kong J. Neurochemical changes in patients with chronic low Back pain detected by proton magnetic resonance spectroscopy: a systematic review. *Neuroimage Clin*. (2017) 13:33–8. doi: 10.1016/j.nicl.2016.11.006

13. Widerstrom-Noga E, Pattany PM, Cruz-Almeida Y, Felix ER, Perez S, Cardenas DD, et al. Metabolite concentrations in the anterior cingulate cortex predict high neuropathic pain impact after spinal cord injury. *Pain*. (2013) 154:204–12. doi: 10.1016/j.pain.2012.07.022

14. Widerstrom-Noga E, Cruz-Almeida Y, Felix ER, Pattany PM. Somatosensory phenotype is associated with thalamic metabolites and pain intensity after spinal cord injury. *Pain*. (2015) 156:166–74. doi: 10.1016/j.pain.0000000000000019

15. Zunhammer M, Schweizer LM, Witte V, Harris RE, Bingel U, Schmidt-Wilcke T. Combined glutamate and glutamine levels in pain-processing brain regions are associated with individual pain sensitivity. *Pain*. (2016) 157:2248–56. doi: 10.1097/j.pain.0000000000000634

16. Wang W, Zhang X, Bai X, Zhang Y, Yuan Z, Tang H, et al. Gamma-aminobutyric acid and glutamate/glutamine levels in the dentate nucleus and periaqueductal gray with episodic and chronic migraine: a proton magnetic resonance spectroscopy study. *J Headache Pain*. (2022) 23:83. doi: 10.1186/s10194-022-01452-6

17. Pigott T, McPeak A, de Chastelain A, DeMayo MM, Rasic N, Rayner L, et al. Changes in brain Gaba and glutamate and improvements in physical functioning following intensive pain rehabilitation in youth with chronic pain. *J Pain*. (2023) 24:1288–97. doi: 10.1016/j.jpain.2023.02.027

18. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM. N-Acetylaspartate in the Cns: from Neurodiagnostics to neurobiology. *Prog Neurobiol*. (2007) 81:89–131. doi: 10.1016/j.pneurobio.2006.12.003

19. Robayo LE, Govind V, Salan T, Cherup NP, Sheriff S, Maudsley AA, et al. Neurometabolite alterations in traumatic brain injury and associations with chronic pain. *Front Neurosci*. (2023) 17:1125128. doi: 10.3389/fnins.2023.1125128

20. Puts NA, Edden RA. *In vivo* magnetic resonance spectroscopy of Gaba: a methodological review. *Prog Nucl Magn Reson Spectrosc*. (2012) 60:29–41. doi: 10.1016/j.pnmrs.2011.06.001

21. Bridge H, Stagg CJ, Near J, Lau CI, Zisner A, Cader MZ. Altered neurochemical coupling in the occipital cortex in migraine with visual Aura. *Cephalalgia*. (2015) 35:1025–30. doi: 10.1177/0333102414566860

22. Shen J, Rothman DL. Magnetic resonance spectroscopic approaches to studying neuronal: glial interactions. *Biol Psychiatry*. (2002) 52:694–700. doi: 10.1016/s0006-3223(02)01502-0

23. Hansen TM, Olesen AE, Simonsen CW, Fischer IW, Lelic D, Drewes AM, et al. Acute metabolic changes associated with analgesic drugs: an Mr spectroscopy study. *J Neuroimaging*. (2016) 26:545–51. doi: 10.1111/jon.12345

24. Hansen TM, Olesen AE, Simonsen CW, Drewes AM, Frokjaer JB. Cingulate metabolites during pain and morphine treatment as assessed by magnetic resonance spectroscopy. *J Pain Res*. (2014) 7:269–76. doi: 10.2147/JPR.S61193

25. Auvichayapat P, Keeratitanont K, Janyachareon T, Auvichayapat N. The effects of transcranial direct current stimulation on metabolite changes at the anterior cingulate cortex in neuropathic pain: a pilot study. *J Pain Res*. (2018) 11:2301–9. doi: 10.2147/JPR.S172920

26. Moxon-Emre I, Daskalakis ZJ, Blumberger DM, Croarkin PE, Lyon RE, Forde NJ, et al. Modulation of dorsolateral prefrontal cortex glutamate/glutamine levels following repetitive transcranial magnetic stimulation in young adults with autism. *Front Neurosci*. (2021) 15:711542. doi: 10.3389/fnins.2021.711542

27. Serrano-Munoz D, Galan-Arriero I, Avila-Martin G, Gomez-Soriano J, Florensa J, Garcia-Peris A, et al. Deficient inhibitory endogenous pain modulation correlates with periaqueductal gray matter metabolites during chronic whiplash injury. *Clin J Pain*. (2019) 35:668–77. doi: 10.1097/AJP.0000000000000722

28. Farrell SF, Cowin GJ, Pedler A, Durbridge G, de Zoete RMJ, Sterling M. Magnetic resonance spectroscopy assessment of brain metabolite concentrations in individuals with chronic whiplash-associated disorder: a cross-sectional study. *Clin J Pain*. (2021) 37:28–37. doi: 10.1097/AJP.0000000000000890

29. Murillo C, Lopez-Sola M, Cagnie B, Sunol M, Smeets R, Coppieters I, et al. Gray matter adaptations to chronic pain in people with whiplash-associated disorders are partially reversed after treatment: a voxel-based morphometry study. *J Pain*. (2024) 25:104471. doi: 10.1016/j.jpain.2024.01.336

30. Wilson M, Andronesi O, Barker PB, Bartha R, Bizzi A, Bolan PJ, et al. Methodological consensus on clinical proton Mrs of the brain: review and recommendations. *Magn Reson Med*. (2019) 82:527–50. doi: 10.1002/mrm.27742

31. Near J, Harris AD, Juchem C, Kreis R, Marjanska M, Oz G, et al. Preprocessing, analysis and quantification in single-voxel magnetic resonance spectroscopy: experts' consensus recommendations. *NMR Biomed*. (2021) 34:e4257. doi: 10.1002/nbm.4257

32. Barthas F, Sellmeijer J, Hugel S, Waltisperger E, Barrot M, Yalcin I. The anterior cingulate cortex is a critical hub for pain-induced depression. *Biol Psychiatry*. (2015) 77:236–45. doi: 10.1016/j.biopsych.2014.08.004

33. Murillo C, Coppieters I, Cagnie B, Bernaers L, Bontinck J, Meeus M, et al. Neural processing of pain-related distress to neck-specific movements in people with chronic whiplash-associated disorders. *Pain*. (2023) 164:1954–64. doi: 10.1097/j.pain.0000000000002890

34. Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain*. (2003) 126:1079–91. doi: 10.1093/brain/awg102

35. World Medical A. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

36. Hartling L, Brison RJ, Ardern C, Pickett W. Prognostic value of the Quebec classification of whiplash-associated disorders. *Spine*. (2001) 26:36–41. doi: 10.1097/00007632-200101010-00008

37. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S, et al. Scientific monograph of the Quebec task force on whiplash-associated disorders: redefining "whiplash" and its management. *Spine (Phila Pa 1976)*. (1995) 20:1S–73S.

38. Shergill Y, Cote P, Shearer H, Wong JJ, Stupar M, Tibbles A, et al. Inter-rater reliability of the Quebec task force classification system for recent-onset whiplash associated disorders. *J Can Chiropr Assoc*. (2021) 65:186–92.

39. Rios-Leon M, Taylor J, Segura-Fragoso A, Barriga-Martin A. Usefulness of the Dn4, S-Lanss and Paindetect screening questionnaires to detect the neuropathic pain components in people with acute whiplash-associated disorders: a cross-sectional study. *Pain Med*. (2023) 25:344–51. doi: 10.1093/pm/pnad165

40. de Andres AJ, Cruces Prado LM, Canos Verdecho MA, Penide Villanueva L, Del Valle HM, Herdman M, et al. Validation of the short form of the brief pain inventory (bpi-sf) in Spanish patients with non-Cancer-related pain. *Pain Pract*. (2015) 15:643–53. doi: 10.1111/papr.12219

41. Cleeland CS. The M. D. Anderson Symptom Inventory User Guide ■ Version 1 (2016). Available at: https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/MDASI_userguide.pdf.

42. Gudala K, Ghai B, Bansal D. Usefulness of four commonly used neuropathic pain screening questionnaires in patients with chronic low Back pain: a cross-sectional study. *Korean J Pain*. (2017) 30:51–8. doi: 10.3344/kjp.2017.30.1.51

43. Shraim MA, Masse-Alarie H, Hodges PW. Methods to discriminate between mechanism-based categories of pain experienced in the musculoskeletal system: a systematic review. *Pain*. (2021) 162:1007–37. doi: 10.1097/j.pain.0000000000002113

44. Kosek E, Clauw D, Nijs J, Baron R, Gilron I, Harris RE, et al. Chronic Nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain*. (2021) 162:2629–34. doi: 10.1097/j.pain.0000000000002324

45. Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DLH, Bouhassira D, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain*. (2016) 157:1599–606. doi: 10.1097/j.pain.0000000000000492

46. Perez C, Galvez R, Huelbes S, Insausti J, Bouhassira D, Diaz S, et al. Validity and reliability of the Spanish version of the Dn4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component. *Health Qual Life Outcomes*. (2007) 5:66. doi: 10.1186/1477-7525-5-66

47. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (Dn4). *Pain*. (2005) 114:29–36. doi: 10.1016/j.pain.2004.12.010

48. Mugler JP 3rd, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-Echo imaging (3d Mp rage). *Magn Reson Med*. (1990) 15:152–7. doi: 10.1002/mrm.1910150117

49. Weerasekera A, Morrissey E, Kim M, Saha A, Lin Y, Alshelh Z, et al. Thalamic Neurometabolite alterations in patients with knee osteoarthritis before and after Total knee replacement. *Pain*. (2021) 162:2014–23. doi: 10.1097/j.pain.0000000000002198

50. Hong D, Rohani Rankouhi S, Thielen JW, van Asten JJA, Norris DG. A comparison of Slaser and Mega-Slaser using simultaneous interleaved Acquisition for Measuring Gaba in the human brain at 7t. *PLoS One*. (2019) 14:e0223702. doi: 10.1371/journal.pone.0223702

51. Edden RA, Puts NA, Barker PB. Macromolecule-suppressed Gaba-edited magnetic resonance spectroscopy at 3t. *Magn Reson Med*. (2012) 68:657–61. doi: 10.1002/mrm.24391

52. Dou W, Speck O, Benner T, Kaufmann J, Li M, Zhong K, et al. Automatic voxel positioning for Mrs at 7 T. *MAGMA*. (2015) 28:259–70. doi: 10.1007/s10334-014-0469-9

53. Ashburner J, Barnes G, Chen C-C, Daunizeau J, Flandin G, Friston K, et al. Spm12 manual. London: University College London (UCL). (2021). Available at: https://www.researchgate.net/publication/355544981_SPM12_Manual#fullTextFileContent. (Accessed July 22, 2024).

54. Friston K. Statistical parametric mapping (SPM). SPM12 ed. (2014). Available at: https://www.fil.ion.ucl.ac.uk/spm/

55. Deelchand D. MRspa: magnetic resonance signal processing and analysis. 1.5th ed (2018) Available at: https://www.cmrr.umn.edu/downloads/mrspa/.

56. The MathWorks Inc. Matlab Version: 9.13.0 (R2022b). Natick, Massachusetts: The MathWorks Inc. (2022). Available at: https://www.mathworks.com.

57. Provencher S. Lcmodel. 6.3rd ed. Automatic quantification of *in vivo* proton MR spectra. Available at: http://s-provencher.com/lcmodel.shtml (2021).

58. Deelchand DK, Auerbach EJ, Marjanska M. Apparent diffusion coefficients of the five major metabolites measured in the human brain *in vivo* at 3t. *Magn Reson Med*. (2018) 79:2896–901. doi: 10.1002/mrm.26969

59. Fundaun J, Kolski M, Baskozos G, Dilley A, Sterling M, Schmid AB. Nerve pathology and neuropathic pain after whiplash injury: a systematic review and Meta-analysis. *Pain*. (2022) 163:e789–811. doi: 10.1097/j.pain.0000000000002509

60. Sterling M. Physiotherapy management of whiplash-associated disorders (wad). *J Physiother*. (2014) 60:5–12. doi: 10.1016/j.jphys.2013.12.004

61. Kumbhare DA, Elzibak AH, Noseworthy MD. Evaluation of chronic pain using magnetic resonance (Mr) neuroimaging approaches: what the clinician needs to know. *Clin J Pain*. (2017) 33:281–90. doi: 10.1097/AJP.0000000000000415

62. Seminowicz DA, Moayedi M. The dorsolateral prefrontal cortex in acute and chronic pain. *J Pain*. (2017) 18:1027–35. doi: 10.1016/j.jpain.2017.03.008

63. Mills EP, Keay KA, Henderson LA. Brainstem pain-modulation circuitry and its plasticity in neuropathic pain: insights from human brain imaging investigations. *Front Pain Res*. (2021) 2:705345. doi: 10.3389/fpain.2021.705345

64. Tracey I. Imaging Pain. *Br J Anaesth*. (2008) 101:32–9. doi: 10.1093/bja/aen102

65. Malfliet A, Coppieters I, Van Wilgen P, Kregel J, De Pauw R, Dolphens M, et al. Brain changes associated with cognitive and emotional factors in chronic pain: a systematic review. *Eur J Pain*. (2017) 21:769–86. doi: 10.1002/ejp.1003

66. Lin A, Andronesi O, Bogner W, Choi IY, Coello E, Cudalbu C, et al. Minimum reporting standards for *in vivo* magnetic resonance spectroscopy (Mrsinmrs): experts' consensus recommendations. *NMR Biomed*. (2021) 34:e4484. doi: 10.1002/nbm.4484

67. Boissoneault J, Sevel L, Letzen J, Robinson M, Staud R. Biomarkers for musculoskeletal pain conditions: use of brain imaging and machine learning. *Curr Rheumatol Rep*. (2017) 19:5. doi: 10.1007/s11926-017-0629-9

68. Aggarwal K, Manso Jimeno M, Ravi KS, Gonzalez G, Geethanath S. Developing and deploying deep learning models in brain magnetic resonance imaging: a review. *NMR Biomed*. (2023) 36:e5014. doi: 10.1002/nbm.5014

69. Zhao D, Grist JT, Rose HEL, Davies NP, Wilson M, MacPherson L, et al. Metabolite selection for machine learning in childhood brain tumour classification. *NMR Biomed*. (2022) 35:e4673. doi: 10.1002/nbm.4673

70. Di Costanzo A, Trojsi F, Tosetti M, Schirmer T, Lechner SM, Popolizio T, et al. Proton Mr spectroscopy of the brain at 3 T: an update. *Eur Radiol*. (2007) 17:1651–62. doi: 10.1007/s00330-006-0546-1

71. Jansen JF, Backes WH, Nicolay K, Kooi ME. 1h Mr spectroscopy of the brain: absolute quantification of metabolites. *Radiology*. (2006) 240:318–32. doi: 10.1148/radiol.2402050314

72. Cruz-Almeida Y, Porges E. Additional considerations for studying brain metabolite levels across pain conditions using proton magnetic resonance spectroscopy. *NeuroImage*. (2021) 224:117392. doi: 10.1016/j.neuroimage.2020.117392

73. Chang L, Ernst T, Poland RE, Jenden DJ. *In vivo* proton magnetic resonance spectroscopy of the normal aging human brain. *Life Sci*. (1996) 58:2049–56. doi: 10.1016/0024-3205(96)00197-x

74. Bliss TV, Collingridge GL, Kaang BK, Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. *Nat Rev Neurosci*. (2016) 17:485–96. doi: 10.1038/nrn.2016.68

75. Benarroch EE. What is the role of the cingulate cortex in pain? *Neurology*. (2020) 95:729–32. doi: 10.1212/WNL.0000000000010712

76. Zhuo M. Molecular mechanisms of pain in the anterior cingulate cortex. *J Neurosci Res*. (2006) 84:927–33. doi: 10.1002/jnr.21003

77. Hart RP, Wade JB, Martelli MF. Cognitive impairment in patients with chronic pain: the significance of stress. *Curr Pain Headache Rep*. (2003) 7:116–26. doi: 10.1007/s11916-003-0021-5

78. Xiao X, Ding M, Zhang YQ. Role of the anterior cingulate cortex in translational pain research. *Neurosci Bull*. (2021) 37:405–22. doi: 10.1007/s12264-020-00615-2

79. Pereira V, Goudet C. Emerging trends in pain modulation by metabotropic glutamate receptors. *Front Mol Neurosci*. (2018) 11:464. doi: 10.3389/fnmol.2018.00464

80. Archibald J, MacMillan EL, Graf C, Kozlowski P, Laule C, Kramer JLK. Metabolite activity in the anterior cingulate cortex during a painful stimulus using functional Mrs. *Sci Rep*. (2020) 10:19218. doi: 10.1038/s41598-020-76263-3

81. Kameda T, Fukui S, Tominaga R, Sekiguchi M, Iwashita N, Ito K, et al. Brain metabolite changes in the anterior cingulate cortex of chronic low Back pain patients and correlations between metabolites and psychological state. *Clin J Pain*. (2018) 34:657–63. doi: 10.1097/AJP.0000000000000583

82. Ito T, Tanaka-Mizuno S, Iwashita N, Tooyama I, Shiino A, Miura K, et al. Proton magnetic resonance spectroscopy assessment of metabolite status of the anterior cingulate cortex in chronic pain patients and healthy controls. *J Pain Res*. (2017) 10:287–93. doi: 10.2147/JPR.S123403

83. Shiers S, Price TJ. Molecular, circuit, and anatomical changes in the prefrontal cortex in chronic pain. *Pain*. (2020) 161:1726–9. doi: 10.1097/j.pain.0000000000001897

84. Ong WY, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. *Mol Neurobiol*. (2019) 56:1137–66. doi: 10.1007/s12035-018-1130-9

85. Loggia ML, Berna C, Kim J, Cahalan CM, Martel MO, Gollub RL, et al. The lateral prefrontal cortex mediates the Hyperalgesic effects of negative cognitions in chronic pain patients. *J Pain*. (2015) 16:692–9. doi: 10.1016/j.jpain.2015.04.003

86. Bell T, Lindner M, Langdon A, Mullins PG, Christakou A. Regional striatal cholinergic involvement in human behavioral flexibility. *J Neurosci*. (2019) 39:5740–9. doi: 10.1523/JNEUROSCI.2110-18.2019

87. Jung C, Ichesco E, Ratai EM, Gonzalez RG, Burdo T, Loggia ML, et al. Magnetic resonance imaging of Neuroinflammation in chronic pain: a role for Astrogliosis? *Pain*. (2020) 161:1555–64. doi: 10.1097/j.pain.0000000000001815

88. Lentz MR, Kim WK, Kim H, Soulas C, Lee V, Venna N, et al. Alterations in brain metabolism during the first year of Hiv infection. *J Neurovirol*. (2011) 17:220–9. doi: 10.1007/s13365-011-0030-9

89. Ferrier J, Bayet-Robert M, Dalmann R, El Guerrab A, Aissouni Y, Graveron-Demilly D, et al. Cholinergic neurotransmission in the posterior insular cortex is altered in preclinical models of neuropathic pain: key role of muscarinic M2 receptors in donepezil-induced Antinociception. *J Neurosci*. (2015) 35:16418–30. doi: 10.1523/JNEUROSCI.1537-15.2015

90. Velazquez R, Ferreira E, Knowles S, Fux C, Rodin A, Winslow W, et al. Lifelong choline supplementation ameliorates Alzheimer's disease pathology and associated cognitive deficits by attenuating microglia activation. *Aging Cell*. (2019) 18:e13037. doi: 10.1111/acel.13037

91. Castillo M, Kwock L, Mukherji SK. Clinical applications of proton Mr spectroscopy. *AJNR Am J Neuroradiol*. (1996) 17:1–15.

92. Nordengen K, Heuser C, Rinholm JE, Matalon R, Gundersen V. Localisation of N-Acetylaspartate in oligodendrocytes/myelin. *Brain Struct Funct*. (2015) 220:899–917. doi: 10.1007/s00429-013-0691-7

93. Grachev ID, Apkarian AV. Chemical heterogeneity of the living human brain: a proton Mr spectroscopy study on the effects of sex, age, and brain region. *NeuroImage*. (2000) 11:554–63. doi: 10.1006/nimg.2000.0557

94. Roalf DR, Sydnor VJ, Woods M, Wolk DA, Scott JC, Reddy R, et al. A quantitative meta-analysis of brain glutamate metabolites in aging. *Neurobiol Aging*. (2020) 95:240–9. doi: 10.1016/j.neurobiolaging.2020.07.015

95. Lind A, Boraxbekk CJ, Petersen ET, Paulson OB, Siebner HR, Marsman A. Regional Myo-inositol, Creatine, and choline levels are higher at older age and scale negatively with visuospatial working memory: a cross-sectional proton Mr spectroscopy study at 7 tesla on Normal cognitive ageing. *J Neurosci*. (2020) 40:8149–59. doi: 10.1523/JNEUROSCI.2883-19.2020

96. Harrell F. Regression modeling Startegies: with applications to linear Odels, logistic and ordinal regression and survival analysis. *2nd* ed. New York: Springer Series in Statistics (SSS). (2015). Available at: https://www.springer.com/series/692.

97. Peek AL, Leaver AM, Foster S, Oeltzschner G, Puts NA, Galloway G, et al. Increased Gaba+ in people with migraine, headache, and pain conditions-a potential marker of pain. *J Pain*. (2021) 22:1631–45. doi: 10.1016/j.jpain.2021.06.005

98. Freitag P, Greenlee MW, Wachter K, Ettlin TM, Radue EW. Fmri response during visual motion stimulation in patients with late whiplash syndrome. *Neurorehabil Neural Repair*. (2001) 15:31–7. doi: 10.1177/154596830101500105

99. Wang WE, Ho RLM, Ribeiro-Dasilva MC, Fillingim RB, Coombes SA. Chronic jaw pain attenuates neural oscillations during motor-evoked pain. *Brain Res*. (2020) 1748:147085. doi: 10.1016/j.brainres.2020.147085

100. Brand A, Richter-Landsberg C, Leibfritz D. Multinuclear Nmr studies on the energy metabolism of glial and neuronal cells. *Dev Neurosci*. (1993) 15:289–98. doi: 10.1159/000111347

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 02 September 2024
DOI 10.3389/fmed.2024.1405188

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OPEN ACCESS

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RECEIVED 22 March 2024
ACCEPTED 28 May 2024
PUBLISHED 02 September 2024

CITATION
Diao Z, Guo D, Zhang J, Zhang R, Li C, Chen H and Ma Y (2024) Causal relationship between modifiable risk factors and knee osteoarthritis: a Mendelian randomization study.
Front. Med. 11:1405188.
doi: 10.3389/fmed.2024.1405188

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Causal relationship between modifiable risk factors and knee osteoarthritis: a Mendelian randomization study

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Background: While several risk factors for knee osteoarthritis (KOA) have been recognized, the pathogenesis of KOA and the causal relationship between modifiable risk factors and KOA in genetic epidemiology remain unclear. This study aimed to determine the causal relationship between KOA and its risk factors.

Methods: Data were obtained from published Genome-Wide Association study (GWAS) databases. A two-sample Mendelian randomization (MR) analysis was performed with genetic variants associated with risk factors as instrumental variables and KOA as outcome. First, inverse variance weighting was used as the main MR analysis method, and then a series of sensitivity analyses were conducted to comprehensively evaluate the causal relationship between them.

Results: Univariate forward MR analysis revealed that genetically predicted hypothyroidism, hyperthyroidism/thyrotoxicosis, educational level, income level, metabolic syndrome (MS), essential hypertension, height, hot drink temperature, diet (abstaining from sugar-sweetened or wheat products), and psychological and psychiatric disorders (stress, depression, and anxiety) were causally associated with KOA. Reverse MR exhibits a causal association between KOA and educational attainment. Multivariate MR analysis adjusted for the inclusion of potential mediators, such as body mass index (BMI), smoking, alcohol consumption, and sex, exhibited some variation in causal effects. However, hyperthyroidism/thyrotoxicosis had a significant causal effect on KOA, and there was good evidence that height, hypothyroidism, educational level, psychological and psychiatric disorders (stress, depression, and anxiety), and abstaining from wheat products had an independent causal relationship. The mediating effect of BMI as a mediator was also identified.

Conclusion: This study used MR to validate the causal relationship between KOA and its risk factors, providing new insights for preventing and treating KOA in clinical practice and for developing public health policies.

KEYWORDS

Mendelian randomization, knee osteoarthritis, risk factors, causal relationship, genetic variants

1 Introduction

Knee osteoarthritis (KOA) is a common type of osteoarthritis (1), and its clinical manifestations include chronic knee pain, limited activity, and dysfunction (2). KOA affects approximately 16% of the population worldwide, and the number of new cases of KOA reached 86.7 million in 2020 (3, 4). Therefore, KOA significantly contributes to disability (5), imposing substantial social and economic burdens and presenting a significant challenge to global public health (6, 7). The pathogenesis of knee osteoarthritis remains unclear. Previous observational studies have found increasing evidence that risk factors such as educational level, economic level (8, 9), metabolic syndrome (MS), essential hypertension (10), thyroid dysfunction (11), diet (12), hot drink temperature (13), height (14), and psychological and mental diseases (such as stress, depression, and anxiety) (15) are associated with the pathogenesis of KOA. Despite this relationship, the causal association obtained from observational studies of traditional epidemiology may be challenging and cannot be used as reliable evidence because residual confounding factors and reverse causality may lead to bias in traditional observational studies (16). Concurrently, large-sample randomized controlled studies are expensive and time-consuming, making them difficult to use in practice.

Mendelian randomization (MR) is an emerging method for inferring causal associations in genetic epidemiology that provides reliable evidence for inferring causal effects between risk factors and outcomes using genetic variants from genome-wide association studies (GWAS) as instrumental variables (IV) (17). Because human genetic variation is characterized by random allocation, irreversibility, and fixity, MR can be used to effectively avoid the influence of confounding factors and reverse causality (18). Thus, univariate MR could be used to estimate the direct causal association between each risk factor and KOA. Multivariate MR is an extension of MR and has great advantages in avoiding unobserved confounding factors and collider biases. It can assess direct effects even when a single nucleotide polymorphism (SNP) is associated with multiple exposures. Multivariate MR can also be used to infer the potentially causal relationship between risk factors and KOA and the effect of mediating factors (19–21). Therefore, this study aimed to investigate the relationship between KOA and thyroid dysfunction, educational level, economic income, MS, essential hypertension, diet, height, hot drink temperature, and psychological and mental disorders (tension, depression, and anxiety) using MR, from the perspective of genetic inheritance.

2 Methods

2.1 Study design

This study follows the Strengthening the Reporting of Observational Studies in Epidemiology using MR (STROBE-MR) reporting guidelines (22, 23) (Supplementary Table S1). In this study, genetic variants significantly associated with exposures were selected as IV to infer causal relationships between exposures and outcomes, and we chose SNPs significantly associated with each risk factor as IVs for the MR analyses. To ensure the validity of IVs, we needed to satisfy the three assumptions of relevance, independence, and exclusivity for MR. Firstly, the genetic variants should be directly associated with the exposures in question. Second, genetic variants should be uncorrelated with any of the other confounders. Third, genetic variants should not be directly related to the outcome (KOA), but should only influence the outcome through exposure (16). In this study, SNPs were obtained from published GWAS data, and causal and sensitivity analyses were performed. Figure 1 shows a schematic of this process.

All data in this study were obtained from published data, and ethical approval for each study was obtained from the appropriate ethics committee. The current study was a secondary analysis of the data and did not therefore require ethical approval. In this study, three types of analyses–namely, two-sample bidirectional MR, multivariate MR, and mediation analyses–were conducted as research methods.

2.2 Data sources

All GWAS data used in this study are available from the IEU OpenGWAS project[1] and FinnGen alliance.[2] The pooled KOA data used in this study were obtained from a large GWAS conducted by Tachmazidou et al. (24), which included 24,955 cases and 378,169 controls from England, Scotland, Wales, and Northern Ireland. Additionally, meta-analysis was performed using GWAS data from the United Kingdom Biobank and arcOGEN database. Based on a comprehensive consideration of previous literature review and clinical observation, the risk factors for KOA included in this study were hyperthyroidism, hypothyroidism, economic income, diet (abstaining from sugar-sweetened or wheat products), height, essential hypertension, educational level, hot drink temperature, psychological and mental disorders (stress, depression, and anxiety), and MS. Educational level was included in both subtypes. Diseases associated with these risk factors were diagnosed according to the International Classification of Diseases-10th Revision criteria. Hot drink temperature was derived from a questionnaire containing the following main question: 'What hot drinks do you prefer (e.g., coffee or tea)?', with the response options being 'very hot', 'hot', 'mildly hot', and 'non-hot' drinks (13). Additionally, genetic variation data on risk factors were provided by the FinnGen Consortium, Medical Research Council Integrative Epidemiology Unit, United Kingdom Biobank, Neale Lab, and Science Genetic Association Consortium (Supplementary Table S2). The present study also included potentially relevant mediators such as BMI, alcohol consumption, smoking, and sex (25–27), with BMI and smoking coming from the United Kingdom Biobank's big data analysis and with alcohol consumption from the GWAS and Sequencing Consortium of Alcohol and Nicotine use. Pooled data on sex were from the combined analysis data of five different cohorts (23andMe, United Kingdom Biobank, iPSYCH, FinnGen, and Biobank Japan), totalling 3,309,398 samples by Pirastu et al. (28).

1 https://gwas.mrcieu.ac.uk/

2 https://r8.finngen.fi/

2.3 Genetic instrument selection

Independent SNPs with thresholds smaller than the genome-wide significance threshold (5×10^{-8}) were selected as IV to ensure the authenticity and reliability of the causal relationship between risk factors and KOA. Simultaneously, to avoid bias caused by linkage disequilibrium among IVs, we used the TwoSampleMR package in R to remove linkage disequilibrium ($R^2 < 0.001$ and clumping distance = 10,000 kb) (29), resulting in a total of 2039 SNPs. The F statistic was employed to evaluate the effects of weak instrumental variables. When $F > 10$, there is no bias caused by the influence of weak IV (30). The F values of the SNPs in this study were > 29.69, providing sufficient evidence that the strong association will not introduce bias. SNP summary data for risk factors are presented in Supplementary Table S3. To ensure that the SNP effects on exposure and outcome correspond to the same alleles and to avoid any distortions in strand orientation or allele coding (31), we excluded SNPs with incompatible alleles and those exhibiting palindromic structures with intermediate allele frequencies. Finally, 14 incompatible alleles and 57 SNPs with palindromic structures were excluded (Supplementary Table S4).

2.4 Statistical analysis

2.4.1 Univariate and multivariate MR analyses

A univariate two-sample bidirectional MR analysis was performed to clarify the direct genetic causality between KOA and its risk factors. In this study, the Wald ratio method was first used to test the causal effect size of each IV on KOA and provide evidence for the identified association (32). Multiple independent and valid IVs were included, and inverse variance weighting (IVW) was used as the main analysis method to test causality. Additionally, to prevent the influence of unknown confounding factors and ensure the reliability of the results, four supplementary analysis methods—weighted median estimation, MR-Egger regression, simple mode, and weighted mode—were used for verification (33). The premise of IVW analysis is that there is no pleiotropy in the IV. Fixed effect IVW is usually used when all

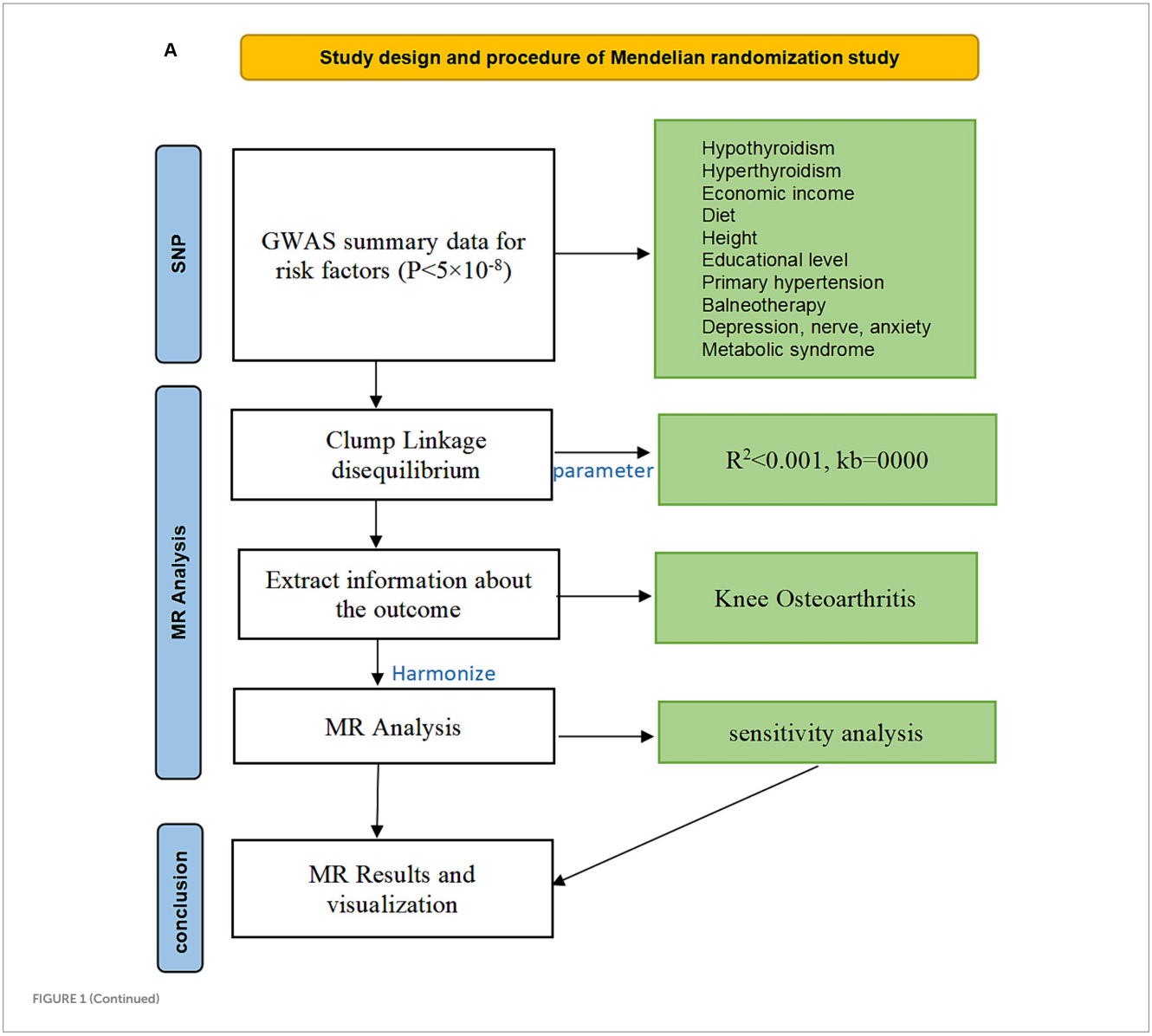

FIGURE 1 (Continued)

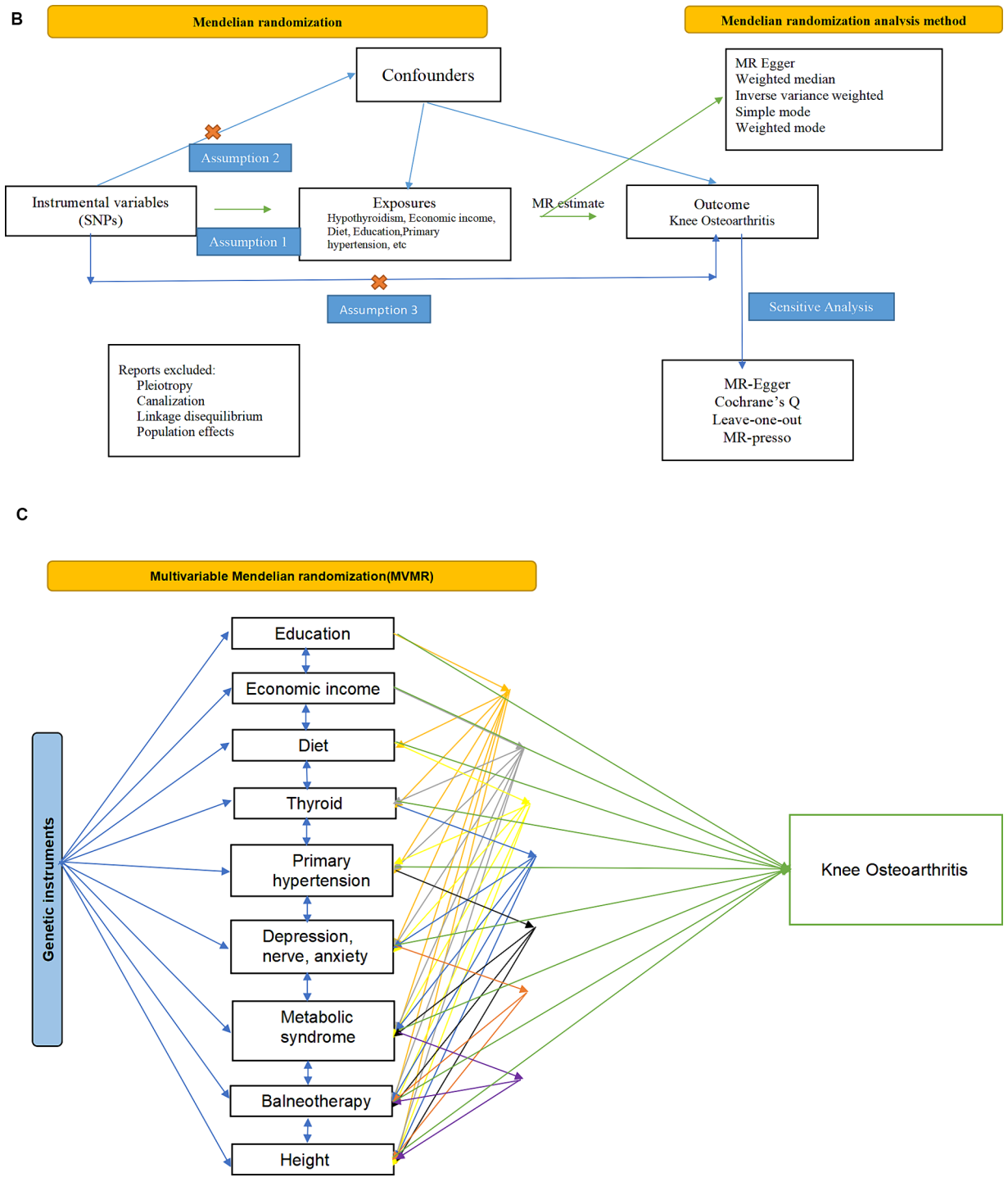

FIGURE 1
Schematic diagram of Mendel randomization research design process. **(A)** Flow chart of Mendelian randomization. **(B)** Univariate two-sample Mendelian randomization analysis of risk factors and KOA. **(C)** Multivariate Mendelian randomization analysis of risk factors and KOA. SNP, single nucleotide polymorphism; KOA, knee osteoarthritis; MR, Mendelian randomization.

included SNPs are valid, and random effect IVW is used only when there is obvious heterogeneity among the SNPs (34–36). When the instrumental strength meets the requirement of independence from the direct effect, the MR-Egger regression test can provide stronger proof for the causal estimate. Additionally, when the intercept of the MR-Egger regression is infinitely close to zero, the result is infinitely close to the IVW (37). Even if up to 50% of the IVs are invalid, the weighted median estimation can still provide robust analytical results (38). Simple and weighted modes ensure that when some IVs are invalid, the results will not be distorted by the influence of bias (39). To further assess the direct causality, mediating effects, and potential horizontal multidirectionality between KOA and thyroid dysfunction,

income, educational level, diet, mental disorders, height, essential hypertension, multiple sclerosis, and other risk factors, all factors (including the four mediators of BMI, smoking, drinking, and sex) were incorporated in the same model, and multivariate MR analysis was conducted based on linear weighted regression IVW and MR-Egger methods to jointly estimate their causal effects on the risk of KOA. However, because more exposures are likely to cause collinearity, the mv-lasso function was applied to remove unnecessary exposures and correct the results. Additionally, the formula $F = (N - k - 1) / k \times R2 / (1 - R2)$ was used to determine whether a weak instrument bias influenced the *F*-value measurement.

2.4.2 Mediation analysis

Multivariate MR results indicated that BMI might be a mediator; hence, mediation analysis was performed using R software in order to further evaluate the mediating effect and mediator share of BMI in the causal relationship between KOA and the risk factors. First, two-sample MR was conducted to ensure that there was a causal relationship between exposure and BMI and between BMI and KOA, and the effect value between exposure and BMI (BetaXZ) was then calculated. Second, multivariate MR was used to examine the effect of BMI as a potential mediator on KOA (BetaZY) and the adjusted effect value between exposure and KOA (BetaXY1). Finally, univariate MR was performed to evaluate the causal effect between exposure and KOA (BetaXY) and to calculate the mediating effect (BetaXZ×BetaZY) and the share of the mediating effect (BetaXZ×BetaZY/BetaXY). Additionally, the coefficient product test was used to calculate the mediating effect and its confidence interval (CI).

2.4.3 Sensitivity analyses

Sensitivity analyses can be used to test whether the causal associations from MR analyses are robust. First, heterogeneity among the IVs was assessed by calculating Cochran's Q value; if significant heterogeneity existed, a random-effects model was used (29). Second, MR-Egger regression was performed, and the *p* value of its intercept was used to test horizontal pleiotropy. Leave-one-out tests were performed to assess whether causal associations were driven by a specific SNP (40). Finally, using MR-PRESSO detection, we re-examined whether level pleiotropy existed, removed the outliers, and corrected the causal effect values (41). We also used R language to visualize the MR analysis results, including scatter, forest, and funnel plots and sensitivity analysis. All statistical analyses were performed using the 'TwoSampleMR', 'MR-PRESSO', 'MendelianRandomization', and 'MVMR' packages of R software version 4.2.2 (The R Foundation for Statistical Computing, Vienna, Austria), with two-sided *p* values <0.05 being considered statistically significant.

3 Results

3.1 Causal effects of risk factors and KOA

Univariate MR analysis revealed that genetically predicted hypothyroidism, hyperthyroidism/thyrotoxicosis, economic income, diet (abstaining from sugar-sweetened or wheat products), height, essential hypertension, educational level, hot drink temperature, mental disorders (stress, depression, and anxiety), and MS were causally associated with KOA (Supplementary Figure S1). The results indicated that hypothyroidism (odds ratio (OR): 5.56, 95% CI: 1.22–25.32, $p = 0.026$), hyperthyroidism/thyrotoxicosis (OR: 711.17, 95% CI: 49.38–10242.78, $p = 1.40E-06$), abstaining from wheat products (OR: 23.89, 95% CI: 5.13–111.22, $p = 5.256E-05$), abstaining from sugar-sweetened products (OR: 6.95, 95% CI: 1.83–26.42, $p = 0.004$), height (OR: 1.09, 95% CI: 1.03–1.17, $p = 0.006$), primary hypertension (OR: 2.11, 95% CI: 1.11–4.02, $p = 0.023$), and MS (OR: 1.13, 95% CI: 1.04–1.22, $p = 0.003$) increased the risk of KOA, whereas income (OR: 0.69, 95% CI: 0.58–0.82, $p = 4.062E-05$), educational level (OR: 0.52, 95% CI: 0.38–0.71, $p = 2.829E-5$), years of schooling(OR: 0.58, 95% CI: 0.52–0.64, $p = 3.254E-24$), hot drink temperature (OR: 0.55, 95% CI: 0.36–0.85, $p = 0.007$), and psychiatric disorders such as stress, depression, and anxiety (OR: 0.37, 95% CI: 0.003–0.47, $p = 0.011$) reduced the risk of KOA (Figure 2; Supplementary Table S5; Supplementary Figure S2). In the reverse MR analysis, KOA was only associated with educational level (OR: 0.96, 95% CI: 0.93–0.99, $p = 0.011$), and no significant evidence was obtained for the causal relationship or association of KOA with hypothyroidism ($p = 0.362$), hyperthyroidism/thyrotoxicosis ($p = 0.662$), income ($p = 0.171$),

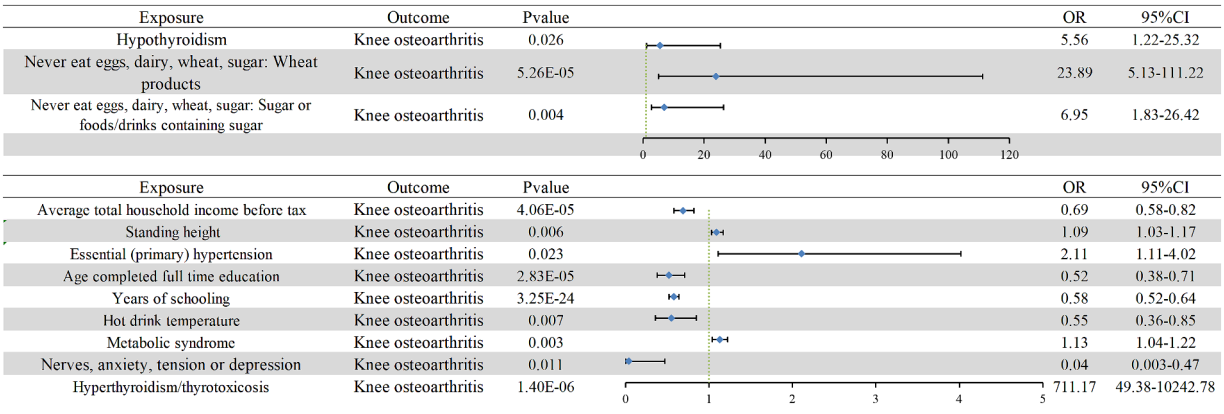

FIGURE 2
Univariate Mendelian randomization results for the causal relationship between KOA and its risk factors. The blue diamond and error line indicate the odds ratio and 95% confidence interval, respectively. OR, odds ratio.

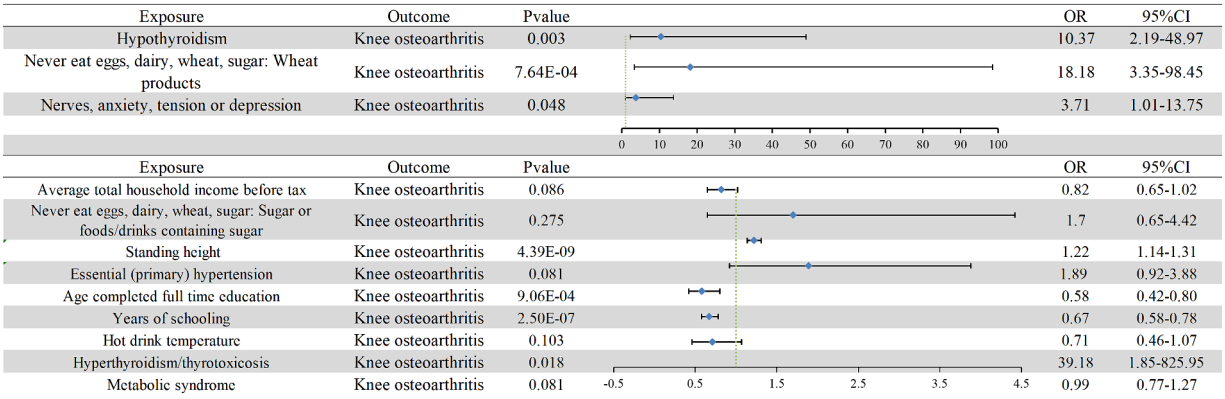

FIGURE 3
Multivariate Mendelian randomization results for the direct causal relationship between KOA and its risk factors. The blue diamond and error line indicate the odds ratio and 95% confidence interval, respectively. OR, odds ratio.

abstinence from sugar-sweetened products ($p = 0.228$), abstaining from wheat products ($p = 0.651$), essential hypertension ($p = 0.533$), MS ($p = 0.675$), height ($p = 0.148$), hot drink temperature ($p = 0.823$), and mental disorders (stress, depression, and anxiety) ($p = 0.447$).

3.2 Multivariate MR analysis

In the multivariate MR model, owing to the potential collinearity problem, we used the mv-lasso function to perform a lasso test (collinearity correction) to correct outliers (34). After incorporating the mediators of BMI, smoking, alcohol consumption, and sex, the adjusted results indicated that hyperthyroidism/thyrotoxicosis (OR: 39.18, 95% CI: 1.85–825.95) had a significant causal relationship with KOA. Sufficient evidence also suggested that hypothyroidism (OR: 10.37, 95% CI: 2.19–48.97), abstaining from wheat products (OR: 18.18, 95% CI: 3.35–98.45), mental disorders (stress, depression, and anxiety) (OR: 3.71, 95% CI: 1.01–13.75), height (OR: 1.22, 95% CI: 1.14–1.31), and educational level (OR: 0.58, 95% CI: 0.42–0.80; OR: 0.67, 95% CI: 0.58–0.78) were casually associated with KOA, whereas essential hypertension (OR: 1.89, 95% CI: 0.92–3.88), MS (OR: 0.99, 95% CI: 0.77–1.27), income (OR: 0.82, 95% CI: 0.65–1.02), hot drink temperature (OR: 0.71, 95% CI: 0.46–1.07), and abstaining from sugar-sweetened products (OR: 1.7, 95% CI: 0.65–4.42) were not statistically significant. Therefore, there was no evidence of a direct effect on the incidence of KOA (Figure 3). In addition, we found in a multivariate MR study that adjusted for smoking, alcohol consumption, and sex were not mediators between risk factors and KOA, and that the true mediator of significance was BMI.

3.3 Sensitivity analyses

The F-statistic for the genetic instrument ranged from 29.69 to 1976.82 (Supplementary Table S3). Therefore, there was sufficient evidence to suggest that a weak instrument bias was unlikely. Heterogeneity tests revealed potential heterogeneity in the causal effect estimates between KOA and hypothyroidism, abstaining from wheat and sugar-sweetened products, height, essential hypertension, educational level, hot drink temperature, MS, and psychiatric disorders (Supplementary Figure S3). A random-effects model was used to estimate the MR effect size, and the results suggested a causal relationship ($p < 0.05$). Based on the evidence of the pleiotropic effect of essential hypertension on KOA, determined by means of the MR-Egger's intercept test, we repeated the MR-PRESSO test after deleting the outliers in the IV, and no significant pleiotropic effect was observed (Supplementary Table S6). Finally, leave-one-out analysis showed that the causal effect between risk factors and KOA was robust (Supplementary Figure S4).

3.4 BMI mediated The genetic predictive effect of risk factors On KOA

Mediation analysis revealed that genetically predicted BMI mediated income (mediation effect = −0.2736; 95% CI: −0.3138, −0.2334; mediated proportion = 73.99%), abstaining from wheat products (mediation effect = 0.9789; 95% CI: 0.6204, 1.3374; mediated proportion = 30.85%), abstinence from sugar-sweetened products (mediation effect = 1.1101; 95% CI: 0.5556, 1.6646; mediated proportion = 57.27%), height (mediation effect = −0.0717; 95% CI: −0.1142, −0.0292; mediated proportion = 99.18%), educational level (mediation effect = −0.2774; 95% CI: −0.3172, −0.2376; mediated proportion = 42.66%; mediation effect = −0.2442; 95% CI: −0.2755, −0.2129; mediated proportion = 44.18%), mental disorders (nerves, anxiety, tension, or depression) (mediation effect = −0.675; 95% CI: −1.0436, −0.3064; mediated proportion = 20.47%), and KOA. (Table 1).

4 Discussion

Currently, the prevention, diagnosis, and treatment of KOA are major challenges for the public health system. In this study, based on large GWAS data, we used an MR analysis system to verify the causal association between 12 KOA-related risk factors and KOA and to determine whether this relationship could be trusted. Single-sample MR analysis based on genetic predictions revealed that

TABLE 1 BMI mediated the genetic predictive effect of risk factors on KOA.

Exposure	Intermediary factors	Outcome	Mediation effect	Proportion of mediation effect	95%CI
Average household income before taxes	BMI	KOA	−0.2736	73.99%	−0.3138, −0.2334
Never eat eggs, dairy, wheat, sugar: Wheat products	BMI	KOA	0.9789	30.85%	0.6204, 1.3374
Never eat eggs, dairy, wheat, sugar: Sugar or foods/drinks containing sugar	BMI	KOA	1.1101	57.27%	0.5556, 1.6646
Standing height	BMI	KOA	−0.0717	99.18%	−0.1142, −0.0292
Age at completion of full-time education	BMI	KOA	−0.2774	42.66%	−0.3172, −0.2376
Education level	BMI	KOA	−0.2442	44.18%	−0.2755, −0.2129
nerves, anxiety, tension or depression	BMI	KOA	−0.6750	20.47%	−1.0436, −0.3064

hypothyroidism, hyperthyroidism/thyrotoxicosis, income, educational level, height, hot drink temperature, diet (abstaining from wheat and sugar-sweetened products), psychiatric disorders (stress, depression, and anxiety), and KOA risk were causal factors. MVMR analyses showed that the causal effects somewhat changed after the inclusion of BMI, sex, smoking, and alcohol consumption and that hyperthyroidism/thyrotoxicosis, essential hypertension, educational level, abstaining from wheat products, and income remained to be significantly causally associated with KOA and could directly influence KOA, whereas height, hot drink temperature, hypothyroidism, abstinence from sugar-sweetened products, depression, and other psychological factors were not directly causally associated with KOA. A mediating factor, BMI, was also identified.

4.1 Thyroid function and KOA

Few observational studies have examined the association between thyroid function and the incidence of KOA. In the Framingham Osteoarthritis Study of 1996, involving 798 women and 577 men, no association was observed between serum thyroid-stimulating hormone (TSH) concentration and KOA. Therefore, there was no evidence that thyroid function was associated with KOA. However, this study only considered serum TSH concentration over a certain period and ignored the development and changes in TSH levels (42, 43). Our MR study made important adjustments, and the results showed that there was a significant positive correlation between hyperthyroidism or hypothyroidism and KOA. A recent retrospective study of 109 patients with thyroid dysfunction who underwent musculoskeletal ultrasound (MSUS) examination and clinical evaluation showed that the knee joint effusion rate, overall MSUS severity score, Visual Analog Scale score, and abnormal frequency of MSUS were significantly higher in patients with thyroid dysfunction, and the imaging examination results were consistent with the clinical evaluation. Therefore, hypothyroidism and hyperthyroidism are causally associated with KOA and could increase the risk of KOA (11). The potential mechanism may be that TSH affects the synthesis of hyaluronic acid and proteoglycans, and increases the viscosity of the knee synovial fluid, leading to KOA-related symptoms (44, 45). Another prospective cohort study also demonstrated that hypothyroidism could cause knee joint degeneration through chondrocalcinosis (46), which is consistent with the results of our MVMR analysis.

4.2 Hypertension, MS, and KOA

Hypertension is an important risk factor for KOA (47, 48), and some recent studies have identified MS as a new risk factor for KOA, which has increasingly gained attention (49, 50). Univariate MR results indicated a causal relationship between MS, hypertension, and KOA; in contrast, multivariate MR analysis showed no statistical significance, which was a somewhat surprising result. We randomly performed mediation analysis and found that BMI mediated the association between MS, essential hypertension, and KOA. A large meta-analysis of four databases–EMBASE, PubMed, Cochrane Library, and MEDLINE–and conference materials, including 1,609 articles, showed that KOA was positively correlated with MS (OR: 1.41, 95% CI: 1.16–1.73) and hypertension (OR: 1.70, 95% CI: 1.411–2.052) in radiology studies and with MS (OR: 1.17, 95% CI: 1.03–1.33) and hypertension (OR: 1.32, 95% CI: 1.18–1.47) in symptomatic studies (10). A previous meta-analysis combined with MR analysis highlighted that hypertension increased the incidence of KOA by 62% and that the association between hypertension and KOA persisted even when the association strength decreased from 3.06 to 1.42 after adjustment for body mass index (BMI) (51). The underlying mechanism may be that hypertension may cause intraosseous hypertension, leading to arterial and venous blockage, reduced bone blood flow, subchondral bone ischaemia, and bone cell apoptosis. Therefore, osteoclasts mediate bone resorption, destroy the mechanical support of the covering cartilage, interfere with the exchange of gasses and metabolites in the bone-cartilage functional unit, and thus induce KOA (52, 53). Concurrently, hypertension can also damage vascular endothelial cells and promote the secretion of prostaglandins, which leads to joint inflammation and cartilage damage (54). A cohort study based on baseline data and controlling for covariates such as sex, race, and BMI not only demonstrated a causal relationship between hypertension and KOA but also demonstrated an association between hypertension and pain in patients with KOA (55). MS is a series of diseases caused by abnormal human metabolism, including central obesity, dyslipidaemia, and insulin resistance (56). However, the mechanisms underlying the relationship between MS and KOA

remain unclear. Inflammatory mechanisms, oxidative stress, the accumulation of advanced glycation end products (AGE), and ectopic lipid deposition in chondrocytes caused by abnormal lipid metabolism can cause KOA (57). Recent studies have shown that macrophages play a key role in this process. On the one hand, MS can promote the polarization of M1 macrophages by acting on AGE and free fatty acids (FFAs) of macrophages, and AGE can increase the transcription of interleukin (IL)-1β by regulating the NF-κB pathway. FFAs bind to toll-like receptor 4 to release pro-inflammatory factors (58, 59), whereas the adipokine leptin activates the JAK2-STAT3 and PI3K-AKT–mTOR pathways in macrophages, promoting a pro-inflammatory phenotype through the secretion of tumor necrosis factor (TNF)-α and IL-1β (60, 61), resulting in chronic inflammatory hyporesponse and cartilage destruction or deformation. On the other hand, MS can increase chondrocyte degradation through AMPK activity inhibition, whereas excessive mTOR activation inhibits chondrocyte autophagy, preventing self-repair and causing knee chondrocyte damage and KOA (62–64).

4.3 Educational attainment, income, and KOA

With respect to the social economy, educational level and income are closely related to KOA onset (9). This is supported by the results of the univariate MR analysis in the present study, which indicated that educational level and income were negatively associated with KOA onset. Nevertheless, no independent effect of income on KOA was observed in multivariate MR, which may be mediated by BMI. A study based on data from the Korean National Health and Nutrition Examination Survey (KNHANES V) found that the risk of KOA was 1.5 times higher for people with low income than for those with high income, and 2.6 times higher for those with a low educational level than for those with college or higher education. These findings did not vary based on sex. The results remained significant after adjusting for confounding factors such as age and BMI, and the imaging findings provided evidence supporting this idea (65). This point of view has also been confirmed in relevant studies in China, the United States, Denmark, and Japan (66–69). The underlying reason may be that people with a lower relative income engage in relatively heavy physical labor, experience more serious wear on the knee joint, and are less willing to seek medical treatment when they experience discomfort in the early stage (66). Educational level was generally positively correlated with income. However, this correlation was not absolute. People with low educational levels are less aware of KOA and related health policies, which cannot be effectively prevented. This is also a potential cause of KOA development and aggravation (70).

4.4 Depression and KOA

Previous studies have found that mental disorders such as depression increase the risk of KOA (71, 72). This was supported by a recent national cohort study, which showed that depression increased the risk of KOA at baseline over a 4-year follow-up and found a bidirectional association between depression and KOA (73). The association between depression and KOA may be explained by the inflammatory immune mechanism, which is related to the production and release of TNF-α, IL-1β, IL-6, and IL-8 (74, 75). Additionally, the proposed bone-brain axis may provide new insights into this association (76). Our MR results showed that psychological factors such as depression were negatively associated with KOA. We also performed reverse MR; however, this was contrary to the above clinical observations and did not achieve the expected results. Therefore, more rigorous clinical trials in genetics should be conducted to verify this association, which is a new direction for future in-depth research.

4.5 Diet and KOA

In this study, we mainly studied the consumption of whole wheat and its products and the consumption of sugar-sweetened products. Univariate and multivariate MR revealed a significant positive correlation between abstaining from whole wheat and its products and the risk of KOA. In other words, the intake of wheat and its derivative products was negatively correlated with the risk of KOA. The results of previous studies were consistent with our MR analysis results (77). Wheat is an important source of dietary grain fiber (78, 79), and it is also part of the grains included in the Mediterranean diet, which can reduce the risk of KOA owing to its high dietary fiber content (80, 81). Presently, there is limited research on the mechanism linking wheat and its products to KOA; however, the whole wheat diet may be associated with a reduced inflammatory response (82), and clinical trials have demonstrated that it can lower blood lipid and cholesterol levels (83), which could impact KOA. The univariate MR analysis of genetic prediction also showed a causal association between sugar deprivation and KOA; however, the multivariate MR analysis showed that this association was not obvious. Therefore, we believe that this association can be due to the existence of mediating factors. The mechanism underlying the relationship between glucose deprivation and KOA remains unclear. Current studies have shown that articular cartilage is an indispensable part of the knee joint, where only chondrocytes reside. The metabolic homeostasis of chondrocytes is related to the structure and function of cartilage tissue. Chondrocytes are required to obtain glucose and oxygen from the subchondral valley and synovial fluid for glucose metabolism (84). If this process leads to an insufficient nutrient supply, the cartilage will be damaged. Approximately 95% of adenosine triphosphate in chondrocytes is produced by glucose metabolism. We hypothesized that prolonged fasting from carbohydrate products may restrict chondrocyte glucose intake, leading to inhibited mitochondrial respiration, overactive or impaired glycolysis, and reduced total adenosine triphosphate production, assuming other factors remain constant (85–87). Therefore, it leads to a glucose metabolism disorder in chondrocytes and destroys the stability of the structure and function of cartilage tissue, leading to joint degeneration (88, 89). Additionally, current experiments have demonstrated that a high-sugar diet can increase the risk of KOA (90). A high-sugar diet can increase the release of free radicals, accelerate the process of degeneration, and increase the production of pro-inflammatory factors, leading to the formation of a local pro-inflammatory environment and increased risk or aggravation of KOA (91). Therefore, sugar should be moderately consumed in daily life.

4.6 Height and KOA

We observed a possible association between height and genetically predicted KOA. A Finnish population-based cohort study that adjusted for confounding factors yielded consistent results (92). Current research has focused on obesity and KOA. Particularly, most studies have focused on the associations among BMI, weight, and KOA. Interestingly, few studies have focused on the causal relationship between height and KOA. Hart et al. incidentally found a positive correlation between height and KOA in knee joint radiological observations in middle-aged British women (93). Presently, the basic index for determining obesity is BMI; however, most researchers consider weight, waist circumference, and fat (94) and ignore the effect of height, especially in patients with KOA having a normal BMI. From a mechanical perspective, leg length is directly proportional to the pressure generated by the knee. In addition, some studies have found that height and upper body weight are closely related to knee cartilage compression (92). Concurrently, some studies have shown that height is closely related to bone morphology and cartilage thickness, which may be a potential factor influencing the relationship between the two (95).

4.7 Hot drink temperature, balneotherapy, and KOA

In daily life, drinking hot drinks helps attenuate the risk of KOA, as compared to cold drinks. Nonetheless, very little research has been conducted on this topic, with a greater focus on balneotherapy and KOA. We found a genetic link between hot drink temperature and KOA, whereas previous studies reported that balneotherapy effectively relieved the symptoms of KOA (96, 97). As a non-drug complementary therapy for KOA, the mechanism of balneotherapy remains unclear; however, balneotherapy has been verified to affect the progression of KOA through thermal, chemical, and mechanical pathways, among which thermal stimulation plays a more important role (98). Matsumoto et al. found that balneotherapy can significantly improve pain, stiffness, and functional limitations of patients and greatly improve their quality of life (99). Moreover, soaking the knee joint in warm water causes a neuroendocrine response through overheating stimulation, which increases the concentration of serum opioid peptides (such as enkephin) to achieve analgesic and sedative effects (100, 101). Heat stimulation also relieves muscle spasms, inflammation, and oxidative stress. A hot mud bath may reduce the release of pro-inflammatory factors IL-1β, TNF-α, and IL-8, increase the level of anti-inflammatory transforming growth factor-β, and increase the level of cortisol to reduce the inflammatory response. Promoting the reduction in serum extracellular heat shock protein 72 kDa levels can also reduce the release of pro-inflammatory factors (102, 103). Cells and microRNAs (miRNAs) can regulate each other. miRNAs play an important role in the pathogenesis of osteoarthritis and have been detected in human synovial fluid. Therefore, miRNAs can be used as both diagnostic markers and therapeutic targets (104, 105). miRNA-181a has a positive correlation with KOA owing to its involvement in cartilage degradation (106), and the upregulation of miRNA-155, miRNA-223, miRNA-181a, and miRNA-146a levels all play a role in the pathogenesis of cartilage damage and synovitis (107). A previous trial found that after mud bath treatment, miRNA-155, miRNA-223, miRNA-181a, and miRNA146a levels in patients with KOA were significantly decreased, suggesting that balneotherapy has a unique therapeutic effect on KOA (108). In our MR study, hydrotherapy was the main focus of balneotherapy, and the multivariate MR results suggest a potential mediating effect. Through literature review, we found that balneotherapy also includes mud therapy; therefore, confounding factors may affect the MR results. Consequently, we included mud therapy in this study. Bath therapy has the advantages of safety and convenience, and as an alternative therapy for KOA, it has a certain effect, which can appropriately reduce the use of non-steroidal anti-inflammatory drugs, as well as reduce pain and certain economic burden for patients with KOA (109), with good economic and social benefits (110).

4.8 Advantages and limitations

This study has several advantages. First, the MR method used was novel and could avoid bias caused by traditional epidemiological observational studies. In this study, we used univariate and multivariate MR analyses to evaluate the causal relationship between risk factors and KOA from genetics and conducted multiple sensitivity analyses to eliminate outliers. A comprehensive assessment of causality makes the results more reliable. Second, we used publicly available large GWAS data to ensure sufficient sample size and reliable results. We also used independent data for validation to avoid an overlap between the exposure and outcome samples (111). Third, the data were obtained from a European population to avoid bias caused by different populations. We used stringent standard screening tool variables to ensure that extreme values did not affect the results.

However, this study had some limitations. First, there was significant heterogeneity between some risk factors and KOA. Although the evaluation using the random-effects model showed that the results were robust, it inevitably posed some challenges to causality. Second, our use of rigorous criteria for the selection of IV might have missed some outcomes. Third, because of the excessive number of risk factors studied, the results from the multivariate MR analysis were inaccurate owing to bias caused by the existence of collinear problems; therefore, our application of the mv-lasso function to solve collinear problems corrected some outliers. Fourth, this study was based on a European population, which limits the generalizability of the results because of genetic differences among ethnic groups. Finally, the results of the MR analysis suggested a causal association; however, further clinical trials are needed to investigate the underlying mechanisms.

4.9 Clinical implications

This study provides an in-depth causal exploration of several potential risk factors for KOA. We found that BMI plays an irreplaceable role as a mediator between risk factors and KOA, which is in line with previous MR and meta-analysis studies on the causal relationship (112–114) between BMI and KOA that found that BMI increases the risk of KOA in line with our-study results. In clinical settings, physicians can emphasize the importance of weight management in KOA prevention and can encourage healthy eating (advising them to avoid prolonged abstinence from wheat products) and regular exercise to reduce obesity and related health problems. By identifying factors that have a clear causal relationship with KOA (hyperthyroidism/thyrotoxicosis, essential hypertension, MS), physicians can be more precise in assessing a patient's risk, and concurrently treating and managing his or her thyroid disease,

hypertension, and MS may help to reduce the risk of KOA. Public health policymakers can build on these findings to develop more targeted prevention and intervention measures, and by improving public health education, the associations between educational attainment and income and KOA risk found in the study remind public health policymakers of the need to consider the impact of socioeconomic factors on health. Policies can target low-income and less-educated populations with more health support and resources. The findings could also be used to develop health education policies for the general public, particularly in the areas of diet and lifestyle, and consideration could be given to incorporating screening and management of thyroid disorders and hypertension into public health programs, as well as raising public awareness of KOA risk factors.

5 Conclusion

In summary, our study systematically analyzed the causal relationships between genetically predicted KOA and thyroid dysfunction, MS, essential hypertension, educational level, income, dietary factors, height, balneotherapy, and psychophysiological factors. This study highlights the impact of modifiable risk factors on KOA and suggests that the use of drugs that interfere with risk factors can also affect the progression of KOA. Therefore, this study provides a new research direction for the prevention and treatment of KOA and information for the formulation of public health policies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

This study was based on publicly available datasets. Ethical review and approval was not required for the study, in accordance with the local legislation and institutional requirements.

Author contributions

ZD: Conceptualization, Methodology, Software, Visualization, Writing – original draft, Writing – review, editing. DG: Formal analysis, Methodology, Resources, Validation, Visualization, Writing – review, editing. JZ: Data curation, Formal analysis, Writing – review, editing. RZ: Validation, Writing – review, editing. CL: Resources, Validation, Writing – review, editing. HC: Data curation, Methodology, Writing. YM: Conceptualization, Funding acquisition, Methodology, Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the fifth batch of special funds for the Training Program for Outstanding Clinical Talents of Traditional Chinese Medicine [National Letter of TCM Education (2022) No. 1]; the Natural Science Foundation of Shandong Province (ZR2021MH373); High Level Traditional Chinese Medicine Key Disciplines of the State Administration of Traditional Chinese Medicine-External Treatment of Traditional Chinese Medicine(zyyzdxk-2023116); Shandong Traditional Chinese Medicine Science and Technology Project (2020Q002); and the Jinan University 20 Funding Project (2020GXRC005).

Acknowledgments

Data for this study were obtained from the FinnGen Consortium, Medical Research Council Integrated Epidemiology Unit (MRC-IEU), United Kingdom Biobank, Neale Lab, Science Genetic Association Consortium, and the IEU OpenGWAS project. The authors acknowledge the efforts of their staff.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1405188/full#supplementary-material

References

1. Bortoluzzi A, Furini F, Scirè CA. Osteoarthritis and its management - epidemiology, nutritional aspects and environmental factors. *Autoimmun Rev*. (2018) 17:1097–104. doi: 10.1016/j.autrev.2018.06.002

2. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. *Lancet*. (2015) 386:376–87. doi: 10.1016/S0140-6736(14)60802-3

3. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. *EClinicalMedicine*. (2020) 29-30:100587. doi: 10.1016/j.eclinm.2020.100587

4. Aw NM, Yeo SJ, Wylde V, Wong SB, Chan D, Thumboo J, et al. Impact of pain sensitisation on the quality of life of patients with knee osteoarthritis. *RMD Open*. (2022) 8:e001938. doi: 10.1136/rmdopen-2021-001938

5. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. (2012) 380:2163–96. doi: 10.1016/S0140-6736(12)61729-2

6. Vina ER, Kwoh CK. Epidemiology of osteoarthritis: literature update. *Curr Opin Rheumatol*. (2018) 30:160–7. doi: 10.1097/BOR.0000000000000479

7. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, et al. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the global burden of disease study 2017. *Ann Rheum Dis*. (2020) 79:819–28. doi: 10.1136/annrheumdis-2019-216515

8. Kang X, Fransen M, Zhang Y, Li H, Ke Y, Lu M, et al. The high prevalence of knee osteoarthritis in a rural Chinese population: the Wuchuan osteoarthritis study. *Arthritis Rheum*. (2009) 61:641–7. doi: 10.1002/art.24464

9. Callahan LF, Cleveland RJ, Shreffler J, Schwartz TA, Schoster B, Randolph R, et al. Associations of educational attainment, occupation and community poverty with knee osteoarthritis in the Johnston County (North Carolina) osteoarthritis project. *Arthritis Res Ther*. (2011) 13:R169. doi: 10.1186/ar3492

10. Xie Y, Zhou W, Zhong Z, Zhao Z, Yu H, Huang Y, et al. Metabolic syndrome, hypertension, and hyperglycemia were positively associated with knee osteoarthritis, while dyslipidemia showed no association with knee osteoarthritis. *Clin Rheumatol*. (2021) 40:711–24. doi: 10.1007/s10067-020-05216-y

11. Kim BY, Kim SS, Park HK, Kim HS. Assessment of the relationship between knee ultrasound and clinical symptoms in patients with thyroid dysfunction. *J Int Med Res*. (2020) 48:7701. doi: 10.1177/0300060519897701

12. Wang H, Ma B. Healthcare and scientific treatment of knee osteoarthritis. *J Healthc Eng*. (2022) 2022:5919686. doi: 10.1155/2022/5919686

13. Dashti HS, Chen A, Daghlas I, Saxena R. Morning diurnal preference and food intake: a Mendelian randomization study. *Am J Clin Nutr*. (2020) 112:1348–57. doi: 10.1093/ajcn/nqaa219

14. Hunter DJ, Niu J, Zhang Y, Nevitt MC, Xu L, Lui LY, et al. Knee height, knee pain, and knee osteoarthritis: the Beijing osteoarthritis study. *Arthritis Rheum*. (2005) 52:1418–23. doi: 10.1002/art.21017

15. Deveza LA, Melo L, Yamato TP, Mills K, Ravi V, Hunter DJ. Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. *Osteoarthr Cartil*. (2017) 25:1926–41. doi: 10.1016/j.joca.2017.08.009

16. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. (2018) 362:k601. doi: 10.1136/bmj.k601

17. Bowden J, Holmes MV. Meta-analysis and Mendelian randomization: a review. *Res Synth Methods*. (2019) 10:486–96. doi: 10.1002/jrsm.1346

18. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. *JAMA*. (2017) 318:1925–6. doi: 10.1001/jama.2017.17219

19. Sanderson E. Multivariable Mendelian randomization and mediation. *Cold Spring Harb Perspect Med*. (2021) 11:a038984. doi: 10.1101/cshperspect.a038984

20. Carter AR, Sanderson E, Hammerton G, Richmond RC, Davey Smith G, Heron J, et al. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. *Eur J Epidemiol*. (2021) 36:465–78. doi: 10.1007/s10654-021-00757-1

21. Sanderson E, Davey Smith G, Windmeijer F, Bowden J. An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. *Int J Epidemiol*. (2019) 48:713–27. doi: 10.1093/ije/dyy262

22. Skrivankova VW, Richmond RC, Woolf BAR, Davies NM, Swanson SA, VanderWeele TJ, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomisation (STROBE-MR): explanation and elaboration. *BMJ*. (2021) 375:n2233. doi: 10.1136/bmj.n2233

23. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: the STROBE-MR statement. *JAMA*. (2021) 326:1614–21. doi: 10.1001/jama.2021.18236

24. Tachmazidou I, Hatzikotoulas K, Southam L, Esparza-Gordillo J, Haberland V, Zheng J, et al. Identification of new therapeutic targets for osteoarthritis through genome-wide analyses of UK biobank data. *Nat Genet*. (2019) 51:230–6. doi: 10.1038/s41588-018-0327-1

25. Hartley A, Sanderson E, Granell R, Paternoster L, Zheng J, Smith GD, et al. Using multivariable Mendelian randomization to estimate the causal effect of bone mineral density on osteoarthritis risk, independently of body mass index. *Int J Epidemiol*. (2022) 51:1254–67. doi: 10.1093/ije/dyab251

26. Larsson SC, Burgess S. Appraising the causal role of smoking in multiple diseases: a systematic review and meta-analysis of Mendelian randomization studies. *EBioMedicine*. (2022) 82:104154. doi: 10.1016/j.ebiom.2022.104154

27. Gill D, Karhunen V, Malik R, Dichgans M, Sofat N. Cardiometabolic traits mediating the effect of education on osteoarthritis risk: a Mendelian randomization study. *Osteoarthr Cartil*. (2021) 29:365–71. doi: 10.1016/j.joca.2020.12.015

28. Pirastu N, Cordioli M, Nandakumar P, Mignogna G, Abdellaoui A, Hollis B, et al. Genetic analyses identify widespread sex-differential participation bias. *Nat Genet*. (2021) 53:663–71. doi: 10.1038/s41588-021-00846-7

29. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-base platform supports systematic causal inference across the human phenome. *eLife*. (2018) 7:e34408. doi: 10.7554/eLife.34408

30. Maciejewski ML, Dowd BE, Norton EC. Instrumental variables and heterogeneous treatment effects. *JAMA*. (2022) 327:1177–8. doi: 10.1001/jama.2022.2505

31. Long Y, Tang L, Zhou Y, Zhao S, Zhu H. Causal relationship between gut microbiota and cancers: a two-sample Mendelian randomisation study. *BMC Med*. (2023) 21:66. doi: 10.1186/s12916-023-02761-6

32. Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. *Stat Methods Med Res*. (2017) 26:2333–55. doi: 10.1177/0962280215597579

33. Liu S, Feng S, Du F, Zhang K, Shen Y. Association of smoking, alcohol, and coffee consumption with the risk of ovarian cancer and prognosis: a Mendelian randomization study. *BMC Cancer*. (2023) 23:256. doi: 10.1186/s12885-023-10737-1

34. Bowden J, Hemani G, Davey Smith G. Invited commentary: detecting individual and global horizontal pleiotropy in mendelian randomization-a job for the humble heterogeneity statistic. *Am J Epidemiol*. (2018) 187:2681–5. doi: 10.1093/aje/kwy185

35. Bowden J, del Greco M F, Minelli C, Davey Smith G, Sheehan N, Thompson J. A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization. *Stat Med*. (2017) 36:1783–802. doi: 10.1002/sim.7221

36. Labrecque J, Swanson SA. Understanding the assumptions underlying instrumental variable analyses: a brief review of falsification strategies and related tools. *Curr Epidemiol Rep*. (2018) 5:214–20. doi: 10.1007/s40471-018-0152-1

37. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. (2015) 44:512–25. doi: 10.1093/ije/dyv080

38. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. (2016) 40:304–14. doi: 10.1002/gepi.21965

39. Hartwig FP, Davey Smith G, Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol*. (2017) 46:1985–98. doi: 10.1093/ije/dyx102

40. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. *Epidemiology*. (2017) 28:30–42. doi: 10.1097/EDE.0000000000000559

41. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet*. (2018) 50:693–8. doi: 10.1038/s41588-018-0099-7

42. Chaisson CE, McAlindon TE, Felson DT, Naimark A, Wilson PW, Sawin CT. Lack of association between thyroid status and chondrocalcinosis or osteoarthritis: the Framingham osteoarthritis study. *J Rheumatol*. (1996) 23:711–5.

43. Hellevik AI, Johnsen MB, Langhammer A, Fenstad AM, Furnes O, Storheim K, et al. Incidence of total hip or knee replacement due to osteoarthritis in relation to thyroid function: a prospective cohort study (the Nord-Trøndelag health study). *BMC Musculoskelet Disord*. (2017) 18:201. doi: 10.1186/s12891-017-1565-6

44. Bland JH, Frymoyer JW, Newberg AH, Revers R, Norman RJ. Rheumatic syndromes in endocrine disease. *Semin Arthritis Rheum*. (1979) 9:23–65. doi: 10.1016/0049-0172(79)90002-7

45. Newcombe DS, Ortel RW, Levey GS. Activation of human synovial membrane adenylate cyclase by thyroid stimulating hormone (TSH). *Biochem Biophys Res Commun*. (1972) 48:201–4. doi: 10.1016/0006-291X(72)90363-4

46. Tagoe CE, Wang W, Wang S, Barbour KE. Association of anti-thyroid antibodies with radiographic knee osteoarthritis and chondrocalcinosis: a NHANES III study. *Ther Adv Musculoskelet Dis*. (2021) 13:5199. doi: 10.1177/1759720X211035199

47. Solak Y, Afsar B, Vaziri ND, Aslan G, Yalcin CE, Covic A, et al. Hypertension as an autoimmune and inflammatory disease. *Hypertens Res*. (2016) 39:567–73. doi: 10.1038/hr.2016.35

48. Zhang YM, Wang J, Liu XG. Association between hypertension and risk of knee osteoarthritis: a meta-analysis of observational studies. *Medicine (Baltimore)*. (2017) 96:e7584. doi: 10.1097/MD.0000000000007584

49. Li H, George DM, Jaarsma RL, Mao X. Metabolic syndrome and components exacerbate osteoarthritis symptoms of pain, depression and reduced knee function. *Ann Transl Med*. (2016) 4:133. doi: 10.21037/atm.2016.03.48

50. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. *Nat Rev Rheumatol*. (2012) 8:729–37. doi: 10.1038/nrrheum.2012.135

51. Lo K, Au M, Ni J, Wen C. Association between hypertension and osteoarthritis: a systematic review and meta-analysis of observational studies. *J Orthop Translat*. (2022) 32:12–20. doi: 10.1016/j.jot.2021.05.003

52. Chan PMB, Wen C, Yang WC, Yan C, Chiu K. Is subchondral bone cyst formation in non-load-bearing region of osteoarthritic knee a vascular problem. *Med Hypotheses*. (2017) 109:80–3. doi: 10.1016/j.mehy.2017.09.027

53. Zhen G, Wen C, Jia X, Li Y, Crane JL, Mears SC, et al. Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis. *Nat Med*. (2013) 19:704–12. doi: 10.1038/nm.3143

54. Velasquez MT, Katz JD. Osteoarthritis: another component of metabolic syndrome. *Metab Syndr Relat Disord*. (2010) 8:295–305. doi: 10.1089/met.2009.0110

55. Shi X, Schlenk EA. Association of hypertension with knee pain severity among people with knee osteoarthritis. *Pain Manag Nurs*. (2022) 23:135–41. doi: 10.1016/j.pmn.2021.08.002

56. Ambroselli D, Masciulli F, Romano E, Catanzaro G, Besharat ZM, Massari MC, et al. New advances in metabolic syndrome, from prevention to treatment: the role of diet and food. *Nutrients*. (2023) 15:640. doi: 10.3390/nu15030640

57. Gao YH, Zhao CW, Liu B, Dong N, Ding L, Li YR, et al. An update on the association between metabolic syndrome and osteoarthritis and on the potential role of leptin in osteoarthritis. *Cytokine*. (2020) 129:155043. doi: 10.1016/j.cyto.2020.155043

58. Kierdorf K, Fritz G. RAGE regulation and signaling in inflammation and beyond. *J Leukoc Biol*. (2013) 94:55–68. doi: 10.1189/jlb.1012519

59. Rogero MM, Calder PC. Obesity, inflammation, toll-like receptor 4 and fatty acids. *Nutrients*. (2018) 10:432. doi: 10.3390/nu10040432

60. Monteiro L, Pereira JADS, Palhinha L, Moraes-Vieira PMM. Leptin in the regulation of the immunometabolism of adipose tissue-macrophages. *J Leukoc Biol*. (2019) 106:703–16. doi: 10.1002/JLB.MR1218-478R

61. Zegeye MM, Lindkvist M, Fälker K, Kumawat AK, Paramel G, Grenegård M, et al. Activation of the JAK/STAT3 and PI3K/AKT pathways are crucial for IL-6 trans-signaling-mediated pro-inflammatory response in human vascular endothelial cells. *Cell Commun Signal*. (2018) 16:55. doi: 10.1186/s12964-018-0268-4

62. Zhou S, Lu W, Chen L, Ge Q, Chen D, Xu Z, et al. AMPK deficiency in chondrocytes accelerated the progression of instability-induced and ageing-associated osteoarthritis in adult mice. *Sci Rep*. (2017) 7:43245. doi: 10.1038/srep43245

63. Terkeltaub R, Yang B, Lotz M, Liu-Bryan R. Chondrocyte AMP-activated protein kinase activity suppresses matrix degradation responses to proinflammatory cytokines interleukin-1β and tumor necrosis factor α. *Arthritis Rheum*. (2011) 63:1928–37. doi: 10.1002/art.30333

64. Dickson BM, Roelofs AJ, Rochford JJ, Wilson HM, De Bari C. The burden of metabolic syndrome on osteoarthritic joints. *Arthritis Res Ther*. (2019) 21:289. doi: 10.1186/s13075-019-2081-x

65. Lee JY, Han K, Park YG, Park SH. Effects of education, income, and occupation on prevalence and symptoms of knee osteoarthritis. *Sci Rep*. (2021) 11:13983. doi: 10.1038/s41598-021-93394-3

66. Liu Y, Zhang H, Liang N, Fan W, Li J, Huang Z, et al. Prevalence and associated factors of knee osteoarthritis in a rural Chinese adult population: an epidemiological survey. *BMC Public Health*. (2016) 16:94. doi: 10.1186/s12889-016-2782-x

67. Vennu V, Abdulrahman TA, Alenazi AM, Bindawas SM. Associations between social determinants and the presence of chronic diseases: data from the osteoarthritis initiative. *BMC Public Health*. (2020) 20:1323. doi: 10.1186/s12889-020-09451-5

68. Jørgensen KT, Pedersen BV, Nielsen NM, Hansen AV, Jacobsen S, Frisch M. Socio-demographic factors, reproductive history and risk of osteoarthritis in a cohort of 4.6 million Danish women and men. *Osteoarthr Cartil*. (2011) 19:1176–82. doi: 10.1016/j.joca.2011.07.009

69. Ikeda T, Aida J, Tsuboya T, Sugiyama K, Kondo K, Osaka K. Psychosocial factors and knee pain among older people in Japan: the JAGES Cross-sectional study. *Clin J Pain*. (2019) 35:983–8. doi: 10.1097/AJP.0000000000000761

70. Aily JB, De Almeida AC, Ramírez PC, Da Silva Alexandre T, Mattiello SM. Lower education is an associated factor with the combination of pain catastrophizing and kinesiophobia in patients with knee osteoarthritis. *Clin Rheumatol*. (2021) 40:2361–7. doi: 10.1007/s10067-020-05518-1

71. Swain S, Coupland C, Mallen C, Kuo CF, Sarmanova A, Bierma-Zeinstra SMA, et al. Temporal relationship between osteoarthritis and comorbidities: a combined case control and cohort study in the UK primary care setting. *Rheumatology (Oxford)*. (2021) 60:4327–39. doi: 10.1093/rheumatology/keab067

72. Vennu V, Misra H, Misra A. Depressive symptoms and the risk of arthritis: a survival analysis using data from the osteoarthritis initiative. *Indian J Psychiatry*. (2019) 61:444–50. doi: 10.4103/psychiatry.IndianJPsychiatry_241_18

73. Lu H, Wang L, Zhou W, Jin S, Chen H, Su Y, et al. Bidirectional association between knee osteoarthritis and depressive symptoms: evidence from a nationwide population-based cohort. *BMC Musculoskelet Disord*. (2022) 23:213. doi: 10.1186/s12891-022-05137-8

74. Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. *Arthritis Res Ther*. (2017) 19:18. doi: 10.1186/s13075-017-1229-9

75. Da Silva MR, Linhares D, Vasconcelos DM, Alves CJ, Neves N, Costa G, et al. Neuroimmune expression in hip osteoarthritis: a systematic review. *BMC Musculoskelet Disord*. (2017) 18:394. doi: 10.1186/s12891-017-1755-2

76. Zhao Y, Suo Y, Yang Z, Hao Y, Li W, Su Y, et al. Inspiration for the prevention and treatment of neuropsychiatric disorders: new insight from the bone-brain-axis. *Brain Res Bull*. (2021) 177:263–72. doi: 10.1016/j.brainresbull.2021.10.009

77. Zertuche JP, Rabasa G, Lichtenstein AH, Matthan NR, Nevitt M, Torner J, et al. Alkylresorcinol, a biomarker for whole grain intake, and its association with osteoarthritis: the MOST study. *Osteoarthr Cartil*. (2022) 30:1337–43. doi: 10.1016/j.joca.2022.07.004

78. Slavin JL, Martini MC, Jacobs DR, Marquart L. Plausible mechanisms for the protectiveness of whole grains. *Am J Clin Nutr*. (1999) 70:459S–63S. doi: 10.1093/ajcn/70.3.459s

79. Liu S. Intake of refined carbohydrates and whole grain foods in relation to risk of type 2 diabetes mellitus and coronary heart disease. *J Am Coll Nutr*. (2002) 21:298–306. doi: 10.1080/07315724.2002.10719227

80. Dai Z, Niu J, Zhang Y, Jacques P, Felson DT. Dietary intake of fibre and risk of knee osteoarthritis in two US prospective cohorts. *Ann Rheum Dis*. (2017) 76:1411–9. doi: 10.1136/annrheumdis-2016-210810

81. Veronese N, Koyanagi A, Stubbs B, Cooper C, Guglielmi G, Rizzoli R, et al. Mediterranean diet and knee osteoarthritis outcomes: a longitudinal cohort study. *Clin Nutr*. (2019) 38:2735–9. doi: 10.1016/j.clnu.2018.11.032

82. Xu Y, Wan Q, Feng J, Du L, Li K, Zhou Y. Whole grain diet reduces systemic inflammation: a meta-analysis of 9 randomized trials. *Medicine (Baltimore)*. (2018) 97:e12995. doi: 10.1097/MD.0000000000012995

83. Sang S, Chu Y. Whole grain oats, more than just a fiber: role of unique phytochemicals. *Mol Nutr Food Res*. (2017) 61:715. doi: 10.1002/mnfr.201600715

84. Marconi A, Hancock-Ronemus A, Gillis JA. Adult chondrogenesis and spontaneous cartilage repair in the skate, *Leucoraja erinacea*. *Elife*. (2020) 9:e53414. doi: 10.7554/eLife.53414

85. Terabe K, Ohashi Y, Tsuchiya S, Ishizuka S, Knudson CB, Knudson W. Chondroprotective effects of 4-methylumbelliferone and hyaluronan synthase-2 overexpression involve changes in chondrocyte energy metabolism. *J Biol Chem*. (2019) 294:17799–817. doi: 10.1074/jbc.RA119.009556

86. Ohashi Y, Takahashi N, Terabe K, Tsuchiya S, Kojima T, Knudson CB, et al. Metabolic reprogramming in chondrocytes to promote mitochondrial respiration reduces downstream features of osteoarthritis. *Sci Rep*. (2021) 11:15131. doi: 10.1038/s41598-021-94611-9

87. Kong P, Chen R, Zou FQ, Wang Y, Liu MC, Wang WG. HIF-1α repairs degenerative chondrocyte glycolytic metabolism by the transcriptional regulation of Runx2. *Eur Rev Med Pharmacol Sci*. (2021) 25:1206–14. doi: 10.26355/eurrev_202102_24823

88. Anderson JR, Chokesuwattanaskul S, Phelan MM, Welting TJM, Lian LY, Peffers MJ, et al. 1H NMR metabolomics identifies underlying inflammatory pathology in osteoarthritis and rheumatoid arthritis synovial joints. *J Proteome Res*. (2018) 17:3780–90. doi: 10.1021/acs.jproteome.8b00455

89. Wei JY, Zhang DM, Xie J, Zhou XD. Research progress in glucose metabolism of chondrocytes. *Sichuan Da Xue Xue Bao Yi Xue Ban*. (2021) 52:923–8. doi: 10.12182/20211160206

90. Min Y, Ahn D, Truong TMT, Kim M, Heo Y, Jee Y, et al. Excessive sucrose exacerbates high fat diet-induced hepatic inflammation and fibrosis promoting osteoarthritis in mice model. *J Nutr Biochem*. (2023) 112:109223. doi: 10.1016/j.jnutbio.2022.109223

91. Ricker MA, Haas WC. Anti-inflammatory diet in clinical practice: a review. *Nutr Clin Pract*. (2017) 32:318–25. doi: 10.1177/0884533617700353

92. Welling M, Auvinen J, Lehenkari P, Männikkö M, Karppinen J, Eskola PJ. Association between height and osteoarthritis of the knee and hip: the northern Finland birth cohort 1966 study. *Int J Rheum Dis*. (2017) 20:1095–104. doi: 10.1111/1756-185X.13059

93. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford study. *Arthritis Rheum*. (1999) 42:17–24. doi: 10.1002/1529-0131(199901)42:1<17::AID-ANR2>3.0.CO;2-E

94. Sun Y, Li Y, Yu T, Zhang J. Causal associations of anthropometric measurements with osteoarthritis: a Mendelian randomization study. *PLoS One*. (2023) 18:e0279198. doi: 10.1371/journal.pone.0279198

95. Schneider MT, Rooks N, Besier T. Cartilage thickness and bone shape variations as a function of sex, height, body mass, and age in young adult knees. *Sci Rep*. (2022) 12:11707. doi: 10.1038/s41598-022-15585-w

96. Varzaityte L, Kubilius R, Rapoliene L, Bartuseviciute R, Balcius A, Ramanauskas K, et al. The effect of balneotherapy and peloid therapy on changes in the functional state of patients with knee joint osteoarthritis: a randomized, controlled, single-blind pilot study. *Int J Biometeorol*. (2020) 64:955–64. doi: 10.1007/s00484-019-01785-z

97. Antonelli M, Donelli D, Fioravanti A. Effects of balneotherapy and spa therapy on quality of life of patients with knee osteoarthritis: a systematic review and meta-analysis. *Rheumatol Int*. (2018) 38:1807–24. doi: 10.1007/s00296-018-4081-6

98. Fioravanti A, Karagülle M, Bender T, Karagülle MZ. Balneotherapy in osteoarthritis: facts, fiction and gaps in knowledge. *Eur J Integr Med*. (2017) 9:148–50. doi: 10.1016/j.eujim.2017.01.001

99. Matsumoto H, Hagino H, Hayashi K, Ideno Y, Wada T, Ogata T, et al. The effect of balneotherapy on pain relief, stiffness, and physical function in patients with osteoarthritis of the knee: a meta-analysis. *Clin Rheumatol*. (2017) 36:1839–47. doi: 10.1007/s10067-017-3592-y

100. Karagülle M, Karagülle MZ, Karagülle O, Dönmez A, Turan M. A 10-day course of SPA therapy is beneficial for people with severe knee osteoarthritis. A 24-week

randomised, controlled pilot study. *Clin Rheumatol*. (2007) 26:2063–71. doi: 10.1007/s10067-007-0618-x

101. Cozzi F, Lazzarin P, Todesco S, Cima L. Hypothalamic-pituitary-adrenal axis dysregulation in healthy subjects undergoing mud-bath applications. *Arthritis Rheum*. (1995) 38:724–5. doi: 10.1002/art.1780380530

102. Ortega E, Gálvez I, Hinchado MD, Guerrero J, Martín-Cordero L, Torres-Piles S. Anti-inflammatory effect as a mechanism of effectiveness underlying the clinical benefits of pelotherapy in osteoarthritis patients: regulation of the altered inflammatory and stress feedback response. *Int J Biometeorol*. (2017) 61:1777–85. doi: 10.1007/s00484-017-1361-x

103. Hou C, Liang L, Chu X, Qin W, Li Y, Zhao Y. The short-term efficacy of mud therapy for knee osteoarthritis: a meta-analysis. *Medicine (Baltimore)*. (2020) 99:e19761. doi: 10.1097/MD.0000000000019761

104. De Palma A, Cheleschi S, Pascarelli NA, Tenti S, Galeazzi M, Fioravanti A. Do MicroRNAs have a key epigenetic role in osteoarthritis and in mechanotransduction. *Clin Exp Rheumatol*. (2017) 35:518–26. doi: 10.1016/j.molmed.2011.11.005

105. Murata K, Yoshitomi H, Tanida S, Ishikawa M, Nishitani K, Ito H, et al. Plasma and synovial fluid microRNAs as potential biomarkers of rheumatoid arthritis and osteoarthritis. *Arthritis Res Ther*. (2010) 12:R86. doi: 10.1186/ar3013

106. Nakamura A, Rampersaud YR, Sharma A, Lewis SJ, Wu B, Datta P, et al. Identification of microRNA-181a-5p and microRNA-4454 as mediators of facet cartilage degeneration. *JCI Insight*. (2016) 1:e86820. doi: 10.1172/jci.insight.86820

107. Okuhara A, Nakasa T, Shibuya H, Niimoto T, Adachi N, Deie M, et al. Changes in microRNA expression in peripheral mononuclear cells according to the progression of osteoarthritis. *Mod Rheumatol*. (2012) 22:446–57. doi: 10.3109/s10165-011-0536-2

108. Giannitti C, de Palma A, Pascarelli NA, Cheleschi S, Giordano N, Galeazzi M, et al. Can balneotherapy modify microRNA expression levels in osteoarthritis? A comparative study in patients with knee osteoarthritis. *Int J Biometeorol*. (2017) 61:2153–8. doi: 10.1007/s00484-017-1420-3

109. Fraioli A, Mennuni G, Fontana M, Nocchi S, Ceccarelli F, Perricone C, et al. Efficacy of spa therapy, mud-pack therapy, balneotherapy, and mud-bath therapy in the management of knee osteoarthritis. A systematic review. *Biomed Res Int*. (2018) 2018:1042576. doi: 10.1155/2018/1042576

110. Ciani O, Pascarelli NA, Giannitti C, Galeazzi M, Meregaglia M, Fattore G, et al. Mud-bath therapy in addition to usual care in bilateral knee osteoarthritis: An economic evaluation alongside a randomized controlled trial. *Arthritis Care Res*. (2017) 69:966–72. doi: 10.1002/acr.23116

111. Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol*. (2016) 40:597–608. doi: 10.1002/gepi.21998

112. He Y, Zheng C, He MH, Huang JR. The causal relationship between body mass index and the risk of osteoarthritis. *Int J Gen Med*. (2021) 14:2227–37. doi: 10.2147/IJGM.S314180

113. Ho J, Mak CCH, Sharma V, To K, Khan W. Mendelian randomization studies of lifestyle-related risk factors for osteoarthritis: a PRISMA review and Meta-analysis. *Int J Mol Sci*. (2022) 23:11906. doi: 10.3390/ijms231911906

114. Thompson WD, Swain S, Zhao SS, Coupland C, Kuo C, Doherty M, et al. Causal associations of central and peripheral risk factors with knee osteoarthritis: a longitudinal and Mendelian randomisation study using UK biobank data. *Pain*. (2024) 2024:3183. doi: 10.1097/j.pain.0000000000003183

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 24 October 2024
DOI 10.3389/fmed.2024.1408693

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RECEIVED 28 March 2024
ACCEPTED 13 September 2024
PUBLISHED 24 October 2024

CITATION
Pasini I, Donisi V, Veneziani E, Perlini C, Nizzero M, Lippolis I, Polati E, Schweiger V and Del Piccolo L (2024) Chronic pain management in fibromyalgia: the INTEGRO (INTEGRated Psychotherapeutic InterventiOn) protocol and its application on two case studies.
Front. Med. 11:1408693.
doi: 10.3389/fmed.2024.1408693

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Chronic pain management in fibromyalgia: the INTEGRO (INTEGRated Psychotherapeutic InterventiOn) protocol and its application on two case studies

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Objectives: To present an innovative integrated manualized psychotherapeutic intervention for fibromyalgia (FM) based on cognitive and behavioral therapy, acceptance and commitment therapy, and somatic experiential techniques (namely the INTEGRated Psychotherapeutic InterventiOn, INTEGRO) and illustrate its application on two case studies.

Methods: INTEGRO is composed of 12 individual sessions. The main objectives of the intervention were psychoeducation of chronic pain mechanisms, understanding the role of cognitive and emotional variables in one's pain perception, teaching patient-tailored skills to increase pain awareness and its management, and learning how to live with pain experience. A 57-year-old woman (patient A) and a 26-year-old woman (patient B) with FM have been selected to describe their care pathways connected to the INTEGRO protocol. Data related to assessment variables and clinical processes have been reported, focusing on the mechanisms that contribute to the maintenance (i.e., avoidance or overcompensation) of chronic pain in FM, on the role of patients' naïf theories, and on the implications that all these aspects may have on the burden related to pain management.

Results: Both patients showed a reduction in FM burden and an increase in self-efficacy in pain management: patient A reported an improvement in emotional regulation ability; patient B showed a decrease in pain interference in work activities and on emotional dimension.

Conclusion: Examining each phase of the clinical protocol through the lens of its clinical application, the paper provides insights into the relationship among crucial psychosocial mechanisms, pain perception, management in FM treatment, and how all these aspects have been dealt with during psychotherapeutic treatment.

KEYWORDS

chronic pain management, fibromyalgia, cognitive behavioral therapy, acceptance and commitment therapy, mind–body intervention, self-efficacy, clinical protocol, health-related quality of life

1 Introduction

Fibromyalgia (FM) is one of the prevalent causes of chronic, widespread pain that primarily affects women (3:1, female-to-male ratio) (1). The prevalence of FM varies depending on the diagnostic criteria used to characterize the disorder, although it generally accounts for 2–3% worldwide (2).

Persons with FM report mainly chronic and diffuse musculoskeletal pain, together with a heterogeneous set of complex poly-symptomatology, such as physical and mental fatigue, anxiety and depressive symptoms, sleep disorders, headache, hypersensitivity to external stimuli, and other functional disorders (3–6). However, the clinical presentation might vary significantly within the same person, by context and time, and among persons themselves (7, 8).

The FM pathogenesis is multifactorial and still needs to be clarified. Several factors should be considered as potential disease triggers (9). One recognized hypothesis describes FM as a central sensitization syndrome characterized by the alteration of nociceptive processes (10–12). However, recent findings support the hypothesis that the disease manifests as stress-related dysautonomia with neuropathic pain features (9, 13). Without reliable and easy-to-use biomarkers for daily clinical practice, self-reported instruments are generally utilized to assess this condition (14). The diagnostic process is often long and complex, contributing to patients' feelings of being invisible, neglected, and "not taken seriously" (15, 16).

The disabling symptoms of FM cause a significant decrease in health-related quality of life (HrQoL), a considerable impact on daily functioning and social interactions, and an increase in emotional distress (17, 18). According to a recent study, the HrQoL categories most affected are "physical pain" and "vitality" (19). Individuals with FM appear to have difficulties in emotion regulation, higher presence of negative affective states, and alterations in enteroception; 60% of persons with FM present a lifetime prevalence of anxiety disorders, while depression is observed in 14–36% of cases (2, 3, 20). Anxiety and depressive symptoms are examples of emotional distress that exacerbates the primary FM symptoms (such as pain, fatigue, and insomnia). This lowers HrQoL and indirectly increases the negative impact of pain on HrQoL (20–22). Moreover, emotional distress, associated with pain-related catastrophic thoughts and fear of pain, contributes to a more intense and aversive pain experience (23, 24). Several studies showed that improved emotional awareness and regulation enhance psychological wellbeing, pain adaptation, positive stress management, and treatment compliance (22, 25–27).

In persons with FM, body perception is characterized by selective and dysfunctional attention to somatic signals, especially those related to painful symptoms, resulting in more significant concerns about their body and avoidance of bodily sensations (28–30).

As regards other psychological variables, self-efficacy and coping strategies have been frequently studied in patients with chronic pain, including FM. Pain-related self-efficacy is associated with better pain adaptation and reduced disability, mediating the effects on the possible development of depressive state symptoms (24, 31, 32). Avoidance, overdoing, and pacing coping strategies result in prevalent approaches to dealing with pain in FM (33). Specifically, pain-related fear leads to avoidance behaviors (34), which, in turn, modify patients' motor patterns, altering body awareness and reducing physical agility (e.g., loss of balance) (29, 35). Distraction and "overdoing" are two examples of avoidance behaviors, whereas the 'pacing' coping strategy, defined as an "activity–rest" cycle or "slow-but-steady" movement (36), appears to be adaptive for chronic pain management (33). Distraction without reframing what happened negatively impacts the severity of the perceived pain (28, 37). Excessive persistence or "overdoing" means that the activity is prolonged or performed at a higher intensity than the patient can tolerate (i.e., when perseverance in the activity permits a task to be completed without a flare-up of discomfort, this appears to be a functional approach; on the contrary, it represents a maladaptive overdoing) (33, 38).

Taking into account the characteristics of FM, treatment should be tailored to the patient and based on a biopsychosocial approach by integrating different components, such as pharmacological and psychosocial treatment, as well as physical activity (39–41).

A growing body of evidence supports the effectiveness of psychological therapy in managing the wide range of cognitive, emotional, and behavioral symptoms associated with FM, with a relevant role for clinical psychologists in the multidisciplinary team for FM treatment. Given the critical role of psychological variables in FM (42), psychotherapy may be beneficial for treating chronic pain (40, 43, 44), with some approaches being especially effective in improving emotion regulation competencies and functional pain-related coping strategies. Specifically, cognitive behavioral therapy (CBT) has been shown to reduce painful symptoms and negative mood deflection and to improve HrQoL and self-efficacy (45, 46) in pain management of FM patients. Acceptance and commitment therapy (ACT) has been shown to enhance the acceptance of pain and reduce pain catastrophizing (47). Body-oriented psychotherapy interventions (i.e., mind–body interventions, embodied cognition approach, and body awareness therapy) also seem to have a positive effect on the management of somatic symptoms related to chronic pain (48) and fibromyalgia syndrome (49, 50). Recently, in the management of FM, practices focused on embodied cognition, based on movement or the perception of it and aimed at reestablishing sensorimotor integration has been considered crucial for fostering reconnection with bodily sensations, promoting a confident and non-judgmental view of one's body (29).

Given the documented relevance and benefits of CBT, ACT, and the recent interest in embodied cognition approaches for pain management, the INTEGRated psychotherapeutic intervention (namely INTEGRO) protocol has been created to help persons with fibromyalgia manage chronic pain (51). The INTEGRO protocol has the peculiarity of integrating, in a manualized treatment, evidence-based practices that help FM patients deal with pain to achieve the following targets:

- To reduce the impact of fibromyalgia symptoms on daily activities by improving HrQoL,
- To lower pain intensity perception,
- To increase perceived self-efficacy in pain management,
- To improve emotional regulation skills.

This study aimed to: (i) describe in detail all steps and topics of the INTEGRO intervention; (ii) show how the implementation of multimodal pain management in clinical practice can be organized by describing the INTEGRO application to two different cases, prototypical of FM patients; (iii) report how the intervention impacts on HrQoL, pain perception, pain-related coping strategies and perceived self-efficacy, psychosocial mechanisms related to pain, emotional regulation skills and body awareness in each of the two patients.

2 Materials and methods

2.1 Procedure

The INTEGRO study 'INTEGRated Psychotherapeutic InterventiOn' is an exploratory longitudinal prospective study (see Pasini et al. (51) for a complete description of the study protocol) and is based on the collaboration between the Clinical Psychological Unit, the Pain Unit, and the Rheumatology Unit of Verona Hospital (Azienda Ospedaliera Universitaria Integrata—AOUI). The study has been approved by the Ethical Committee of Verona Hospital (Prot n. 54513, 12/09/2022). The medical staff of the Pain Unit and the Rheumatology Unit recruit patients who meet the inclusion criteria (i.e., FM diagnosis according to established ACR criteria—American College of Rheumatology (52), and idiopathic chronic pain; 18–65 years old; Italian-speaking; able to provide informed consent).

After being selected, patients sign the informed consent form before participating.

The timeline and procedure of the INTEGRO protocol are reported in detail in Figure 1.

2.2 INTEGRO assessment

Each patient was assessed by using the following instruments:

- Revised Fibromyalgia Impact Questionnaire (FIQ-R) Italian version (53, 54) to evaluate functioning, symptoms, and impact on daily activities (HrQoL) of FM;
- McGill Pain Questionnaire (MPQ) Italian version (55, 56) and the Brief Pain Inventory (BPI) Italian version (57–60) to measure pain intensity perception and different components of pain;
- Pain Self-Efficacy Questionnaire (PSEQ) Italian version (61, 62) to evaluate self-efficacy in chronic pain management;
- Difficulties in Emotion Regulation Scale (DERS) Italian version (26, 63) to assess emotion dysregulation and the acquired skills to reduce it.

The evaluation of pain using the MPQ has been performed at T0, T2, T5, T9, and T12.

The pre- and post-assessment of the other psychosocial variables was conducted before the intervention (T0) and 1 week before the end of treatment (T13).

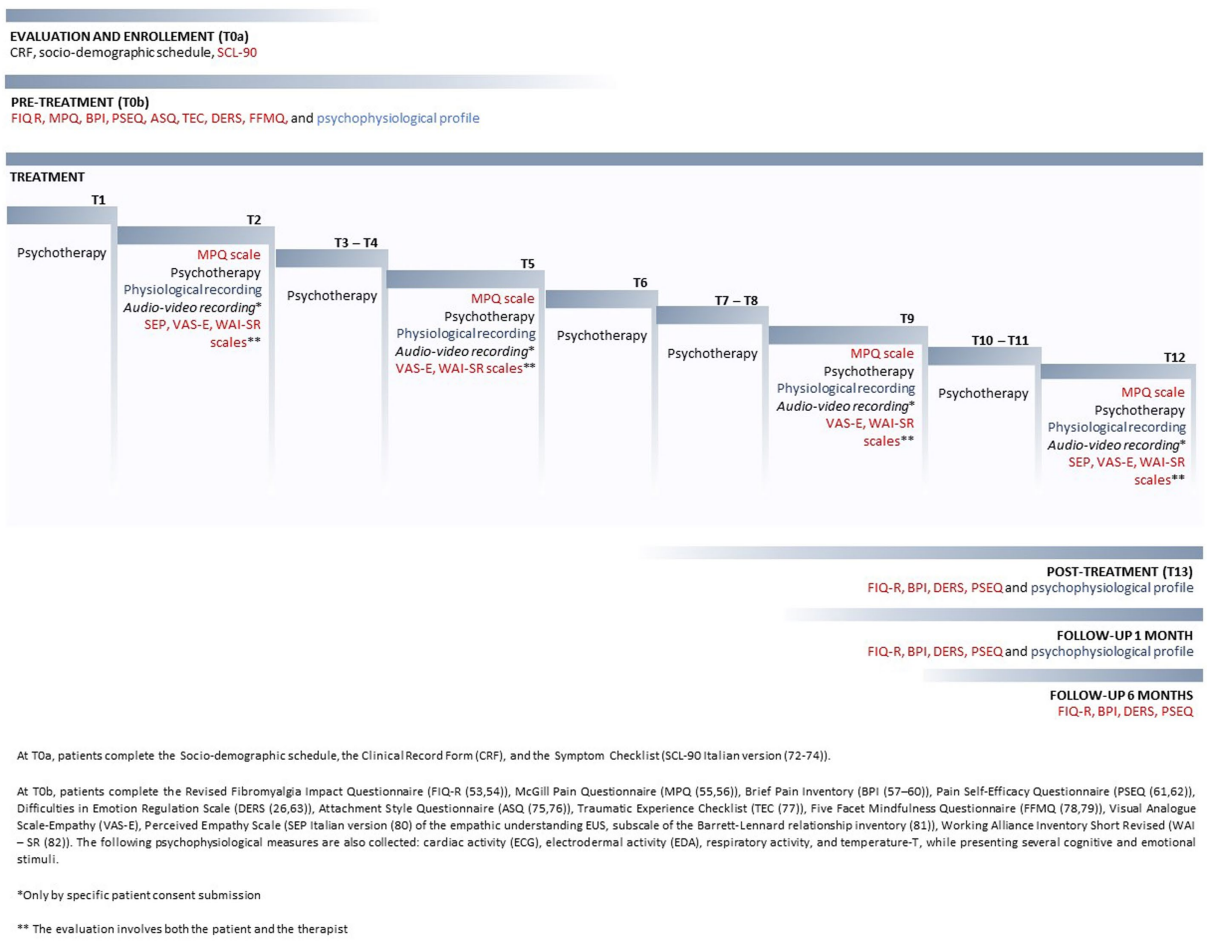

FIGURE 1
Timeline and procedure of the INTEGRO protocol.

For more details on all questionnaires adopted in the INTEGRO study, see Pasini et al. (51).

2.3 Description of the INTEGRO intervention

INTEGRO is implemented in the Clinical Psychology Unit of the Verona University Hospital, Italy, and is led by two clinical psychologists skilled in CBT and ACT and trained in the application of relaxation and mindfulness-based approaches with expertise in chronic pain management.

The intervention is structured in three phases and comprises 12 sessions of 1 h each, performed every 7 or 15 days, according to the patient's needs. Clinical psychologists manage the intervention according to a manualized protocol containing specific aims, topics, and exercises for each session.

The principal steps of the intervention are described in Table 1.

TABLE 1 INTEGRO intervention's main characteristics.

Phase 1—Engagement, Motivation, Psychoeducation
Sessions 1–2—**Description of pain history, theories, and experiences related to disease and introduction to pain mechanisms**. **Promote pain awareness** using the **McGill Pain Questionnaire (MPQ)** and pain monitoring log (i.e., antecedent to the onset of the painful symptom, possible triggering factors, related thoughts, emotions and physical sensations, pain reaction, and outcomes). **Psychoeducation on pain** (e.g., evolutive functions of pain, sensory, cognitive, affective, and behavioral components of pain, mechanisms of functioning) that aims to help the patient recognize pain components through a specific pain monitoring log (created *ad hoc* for INTEGRO).
Sessions 3—**Psychoeducation on chronic pain** (e.g., the difference between acute and chronic pain, central sensitization and alterations of pain inhibitory mechanisms, the role of perception in the experience of pain). **To promote awareness of pain-related cognitive mechanisms** by using a pain monitoring log (created *ad hoc* for INTEGRO).
Session 4—**Pain maintenance mechanisms** (i.e., presence of pain management strategies based on the control paradigm, pain maintenance cycles related to discouragement/depression, anger, anxiety, and fear, both using illustrative graphic representations and through the construction of one's schemes)
Session 5—**Pain communication** (i.e., the patient learns how to communicate one's needs and states of distress, interpersonal cycles of rejection, and distancing or over-caring) Self-awareness of interpersonal cycles can be achieved using graphical representations (forms created *ad hoc* for INTEGRO). Promote awareness of current pain using the **MPQ** Scale.
Session 6—**Coping strategies** (i.e., the patient becomes aware of personal coping strategies and protective behaviors by using graphic representations showing stress-pain and vicious maintenance cycles) (e.g., rumination, hyperarousal, and avoidance) (forms created *ad hoc* for INTEGRO). **Learning the distinction between "clean" pain** ("nociceptive pain") **and "dirty" pain** (the subjective sensation related to the pain that inhibits our life) through the patient's reports and pain monitoring log [forms created *ad hoc* for INTEGRO and partially modified from Joann and Lundgren (69)].
Phase 2—Cognitive Restructuring, Avoidance Reduction, Promotion of Alternative Behavioral Strategies, Experiential Awareness Techniques, and Defusion
Session 7—**Body awareness** (i.e., to promote the distinction between "clean" and "dirty" pain using a specific log in which the patient describes the situational antecedent, clean pain vs. dirty pain intensity; to reduce avoidance and to promote alternative behavioral strategies; to introduce body awareness techniques to recognize and distinguish somatic signals with the aim of appropriately regulate them). **To help the patient understand her relationship with her body** regarding emotions and sensations, she should observe what can be perceived through the body (without focusing on painful sensations) and use grounding resources [adapted from Ogden and Fisher (70)].
Session 8—**Awareness of body sensations to improve relaxation skills** (i.e., psychoeducation on the physiological component of emotions to improve awareness of bodily sensations and their variation in stressful situations) **Embodied techniques** to improve relaxation skills focused on body temperature.
Session 9—**Value orientation** (i.e., to help the patient identify her values and actions in line with her values). To promote awareness of current pain using the **MPQ Scale**, evaluating how the ability to recognize bodily sensations is evolving.
Session 10—**Cognitive defusing to promote pain acceptance** **Use of embodied techniques focused on the breath** to identify somatic centering resources [adapted from Ogden and Fisher (70)]. **Introduction of embodied techniques to explore the qualities of pain** and not be judgmental toward pain [forms created *ad hoc* for INTEGRO and partially modified from Marchi and Blasutti (71)].
Session 11—**Pain acceptance** (i.e., cognitive defusing using a pain log) [forms created *ad hoc* for INTEGRO and partially modified from Joann and Lundgren (69)]. **Embodied techniques to accept pain**, welcoming pain in its characteristics, observing it without judgment, and guiding the breath through it.
Phase 3—Conclusion
Session 12—**Definition of own toolkit for pain management** (i.e., sharing of the objectives achieved during the treatment and identification of the tools acquired; consideration of the difference between acceptance and resignation, also through an imaginative exercise) Value the awareness of current pain using the **MPQ Scale** and how it is evolving, underlining the changeability of pain and the skills acquired by the patient to distinguish pain components.

2.4 Description of the two patients selected to explain how INTEGRO protocol works

Two patients were selected from the study to show how different strategies for dealing with FM symptoms can be managed within the INTEGRO protocol.

Case 1—Patient A:

- Patient A is a 57-year-old woman who lives alone and is unmarried. She works as a professional nurse. FM was diagnosed when she was 55 years old, although the pain began 2 years earlier.
- *Characteristics of pain and fibromyalgia*: Reported symptoms included poly-district pain, the continuous and diffuse hitch that primarily affected the lower and upper limbs, pelvic area, and craniofacial area; severe asthenia; muscle fatigue; cognitive deficit (reduction in concentration, memory, and attention); non-restorative sleep; paresthesia; significant qualitative changes in vision; poor tolerance to various foods; constant profuse sweats accompanied by nausea; and a feeling of deep anguish.
- *Medical–surgical history*: Clinical history is characterized by significant psychological suffering as a result of traumatic events (in childhood and early adulthood), mechanistic arthropathy (polyarthritis) supported by the effects of ligamentous hyperlaxity-type Ehlers–Danlos syndrome, spondylolysis, spondylolisthesis (L5/S1) due to recurrent lumbago; bilateral gonarthrotic pain, musculoskeletal headache, and migraine with aura (adolescent onset), three traumatic brain injuries; removal of myxoid liposarcoma in the right lower limb and local radiotherapy, with the removal of the soleus muscle and sclerosis of the surrounding soft tissues. The subsequent alteration of the skeletal alignment has accentuated the preexisting widespread pain in the compensatory postural phase and made it necessary to use a walking aid.
- *Pharmacological and non-pharmacological treatments and their efficacy*: The patient underwent cycles of hydrokinetic therapy and free body gymnastics for deep muscle building, with moderate results. She is treated with duloxetine (60 mg + 30 mg), quetiapine (25 mg), pregabalin (3× 25 mg), and ibuprofen at need, with 50–70% perceived pain relief.
- *Functional, emotional, and cognitive impact on the patient*: Patient A is currently on sick leave. She plans to apply for early retirement due to a significant impairment in her ability to perform daily activities (e.g., she is unable to drive autonomously and requires specific assistive devices for mobility). Friends give her social support, whereas her brother rarely does.

Case 2—Patient B:

- Patient B is a 26-year-old woman who works as a clerk, is single, and lives with her parents. The diagnosis of FM was confirmed in 2021, but the onset of pain traces back to childhood and worsened during the previous year.
- *Characteristics of pain and fibromyalgia:* Reported symptoms include widespread pain, specifically in the cephalic and cervical area, upper limbs, and rarely in lower limbs, chronic pelvic pain, lumbago, fatigue, cognitive impairment, non-restorative sleep, the feeling of swelling in the hands, auditory sensory losses, and poor tolerance to various foods.
- *Medical–surgical history*: clinical history is characterized by numerous admissions to the Emergency Service without apparent evidence, a significant episode of psychological suffering due to a traumatic event (in early adulthood); irritable bowel syndrome, medically unexplained ligamentous laxity, cervical C3-C4 disk protrusions in the absence of radiculopathy, adenomyosis in extra-progestin therapy, bilateral labyrinthitis, and infectious mononucleosis in 2018. She also underwent surgery for adenoidectomy and bilateral inguinal hernioplasty at a young age. In 2021, a few months after the diagnosis of FM, she reported a minor road injury that was followed by a minor cervical distractive injury.
- *Pharmacological and non-pharmacological treatments and their efficacy*: The patient underwent several physical therapies, such as a cycle of magnetotherapy, without any efficacy. She is treated with therapeutic cannabis—CBD 8–10% (10 drops daily use), Paracetamol (1,000 mg daily use), Diazepam, and NSAIDs at need, with 60% perceived pain relief.
- *Functional, emotional, and cognitive impact on the patient*: Parents give her solid social support, while she feels discouraged and fears judgment from friends and colleagues.

3 Results

3.1 Changes observed in the two selected patients during the INTEGRO therapeutic intervention

This section describes the clinical progression of each selected patient by reporting the main qualitative changes according to the topics and the steps that define the INTEGRO intervention: pain description and perception, pain mechanisms and coping strategies to manage pain, pain and interpersonal relationships, exploration of "clean and dirty pain," body awareness, pain acceptance, cognitive defusing, and value orientation. Differences and commonalities among patient A and patient B for each thematic area of the intervention have been detailed.

3.1.1 Pain description and perception

Patient A experienced intense pain during the morning, with greater rigidity and gradual worsening throughout the day. Going to work or engaging in any activity requiring continuous hand use and/or physical activity (such as shopping, gardening, or physical exercise) worsened the pain.

In patient B, the pain reached the maximum intensity toward evening; at this time of the day, she felt wholly rigid and contracted. When the same posture was held for more than 15 to 20 min, the pain worsened, and it was frequently necessary to stand up or remain in a standing position. This phenomenon also occurred throughout the INTEGRO intervention sessions. Even routine tasks like smiling, blow drying their hair, and tanning determined an increase in the intensity of pain.

3.1.2 Pain mechanisms and coping strategies to manage pain

When discussing approaches to coping and pain mechanisms in sessions 3–6, both patients reported pain management strategies such as overinvestment or avoidance. However, they used those coping strategies with a different frequency.

In patient A, the main pain-coping strategies were ignoring the pain and persisting with tasks beyond the perceived limit, rest, distraction, containing and demoralizing, and medication use (even with preventive purposes). The most used strategy was overinvestment in managing pain, rigidly continuing with the activity she was doing even at the cost of worsening the pain intensity. In these situations, she was aware that she had reached physical limits (i.e., physical fatigue and pain in her hands) but did not stop, addressing herself with anger and criticism to continue the activity (i.e., by saying to herself: "*You have no excuse*"; "*You're just a lazy brat*") and subsequently reporting physical exhaustion, depressed mood, and inability to move limbs due to perceived pain. Continuous ruminating on how frequently she had accomplished her objectives resulted in greater arousal, muscle stiffness, tension, a sense of the head on fire, and torn muscles. This process made it difficult for the patient to manage her resources, causing her to avoid activities relevant to her health. A significant amount of time had to be spent within the clinical protocol examining and comprehending the pain-related vicious cycles, emphasizing the cost associated with the patient's overdoing mechanisms. Only in the last sessions did patient A gain the ability to recognize her overdoing mechanism and to decrease the tendency to apply it as an automatic mechanism.

The prevalent pain management strategies of patient B included ignoring the pain, avoiding behaviors, using medication, increasing physical activity, and controlling nutrition. She was inclined to stay away from social events because of worry that she would become unwell in an environment where no one was familiar with her disease. Indeed, in these situations, the fear of being judged as different and of little value prevailed. Avoiding social situations was also prompted by dysfunctional thoughts about the possible consequences: "*If others see that I am sick, they will exclude me*." This increased the sense of frustration and the idea of being in the "*prison of pain*." Such thoughts were related to feelings of panic, anxiety, and fear and, subsequently, to a significant increase in excitement, muscle tension, and physical stiffness, which, in turn, amplified the perceived pain. Significant avoidance of body signals, including pain, was also present to pander to the primary need for social approval. This pattern was also evident in ignoring body awareness exercises performed during sessions. In the subsequent sessions, patient B gained the ability to recognize painful avoidance behaviors and catastrophic thoughts through pain monitoring exercises. By recognizing her pain management strategies, she was able to think through the effects of these processes and begin to employ alternative coping strategies (i.e., exposing herself to fearful situations and not preemptively giving up on pleasant experiences).

3.1.3 Pain and interpersonal relationships

Patient A focused on caring for others rather than herself and did not perceive it possible to ask others for help. She could share thoughts about FM only in the friend network, but she did not ask for support due to the fear of being judged negatively. This mechanism progressively increased social withdrawal, self-criticism, poor self-efficacy, sadness, and anger toward herself. The only people the patient felt she could share her experience with were healthcare professionals.

Patient B tended to rely heavily on family care, showing an addictive attitude toward them, triggering a cycle of overcaring, thus strengthening the idea of not being able to manage the pain independently. Toward friends and colleagues, she presented feelings of distrust mainly related to the fear of not being understood, rescued, or being judged weak. This attitude reinforced the need to control the pain symptoms, resulting in an increased likelihood of experiencing anxiety, as well as social isolation and reduced positive experiences.

Both patients reported a history of invalidation of their pain by significant ones. Therefore, in all subsequent intervention sessions, it was necessary to pay attention to interpersonal issues (tendency toward selflessness in patient A and social, emotional, and experiential avoidance in patient B). Both patients showed greater awareness of their interpersonal patterns and an initial drive for change during the therapeutic sessions.

3.1.4 Exploration of pain: "*clean and dirty pain*"

Patient A quickly learned to identify the "*dirty pain*" component (e.g., in the constant judgmental and self-punishing demands she made on herself) and its consequences in terms of increased perceived pain and negative impact on daily functioning. Interestingly, in later sessions of the clinical protocol, the patient reported moments in which she did not recognize an initial '*clean*' component of pain. Still, she was able to recognize the emotional component defined by a sense of helplessness, overwhelm, and high anxiety. This key could also be related to the naïve theory of her illness: the belief that the emotional component played an essential role in the symptomatologic onset and maintenance of pain.

Patient B's naïve theory of her illness was mainly based on organic causes without an apparent symptomatologic onset. The patient tried not to pay attention to her pain, being afraid of identifying its presence. This was also evident in the inconsistent completion of the "*clean and dirty pain*" diary between the INTEGRO sessions. Despite the difficulty of distinguishing between the emotional and physical components of pain, especially when it was very intense, the patient was able to identify dirty pain in fear reactions and in the tendency to run away. Therefore, during the treatment, special attention was given to the distinction between the two components of "*clean and dirty*" pain by helping the patient recognize those components and their related emotional function.

3.1.5 Body awareness

At the beginning of phase 2, both patients expressed initial skepticism about the feasibility of performing activities that entailed "*'being' with one's body without seeking to avoid any sensations*" as suggested by the ACT approach. Indeed, for both patients listening to physical sensations was directly associated with pain perception. This belief that observing physical stimuli could contribute to pain-increased perception was associated with anxiety feelings (which

caused panic attacks in patient B). Moreover, looking at other factors associated with pain, in both cases, the painful perception was exacerbated by environmental stimuli (e.g., poor light conditions, cold, and humidity) or emotional factors (e.g., anxiety or fear; depressed mood).

Despite these difficulties, patient A tried to listen to body sensations, at least in situations not perceived as risky. For example, after a few sessions, she could focus on and describe the pain in her leg: *'I have the feeling that I can see myself inside the tissues, the ligaments as if I can observe fiber by fiber...I can move freely in this space...I sit in a kind of neutral basin but close enough to the area of pain: it's a 'big dark, dense, molasses-like mass, dangling between tissues...it sticks here and there...'*

Patient B, especially in the first sessions, struggled to stay in touch with her bodily sensations (i.e., stating that the more she tried to relax, the more her body stiffened and felt a sense of nausea). She tended to control her internal states because of the fear that something irreparable might happen. Although she benefited from the proposed exercises, she tended to become distracted in the first few sessions and did not persist in practicing them at home. During the first exercises to manage pain, she reported: *'I cannot be around it; this damn nausea overrides everything... it disgusts me.'* Only as the exercises progressed did the patient consider that she could observe what was happening in her body without feeling the need to control it, fostering acceptance of the pain: *"By focusing on the breath, I can imagine the pain flowing through the body."*

3.1.6 Pain acceptance, cognitive defusion, and value orientation

By the end of phase 2, patient A improved awareness of how some actions ideally designed to protect her from pain instead moved her away from a life based on desired values. By using "*defusing*" strategies on thoughts related to dirty pain, she learned to slow down when she perceived a painful sensation, to be in contact with the pain and have a clear, non-fearful representation of pain, and to perceive herself as able to continue to live with the pain and carry out, according to her limitations, acting in line with her values.

Patient B realized how obsessively her life focused on preventing pain (perceived as a prison that distanced her from the freedom to choose her own life). The intervention helped her to identify the costs of this struggle and to distance herself from thoughts and emotions related to "dirty pain." By embracing a certain amount of risk and rediscovering some of the previously avoided life events, it was possible to tolerate the unpredictable nature of pain and increase one's self-efficacy while dealing with it.

In the last sessions, both patients showed an improvement in cognitive "*defusing*" ability by accepting pain as a disturbing but not limiting presence. This awareness allowed them to actively identify which strategies could be more functional for specific pain experiences. Patient A reported an improvement in self-care and pacing strategies, a decrease in dysfunctional overdoing, and preventive use of drugs by becoming aware that she could "shape her pain through experiential techniques." Patient B showed a reduction of avoidance and increased social exposure, assertive communication of their own needs, and the use of relaxation techniques to reduce the perception of pain.

3.2 Evaluations along the INTEGRO intervention

This section describes quantitative and qualitative variations in INTEGRO measures.

3.2.1 Pain intensity and quality

In the first sessions, patient A reported large and overlapping pain locations (sessions 1 and 2) (see Figure 2). She used a wide range of pain descriptors (i.e., Number of Words Chosen—NWC) in the MPQ Scale (such as flickering, jumping, pricking, tender, exhausting, sickening, fearful, and wretched). She also described the pain in the hands as 'flaming flows', while pain in the feet as "moving insects." Contact with surfaces caused pain, and sitting on the bed or in chairs was difficult. The difficulty of choosing certain words or body parts appeared to be related to challenges relevant to pain moment-by-moment awareness, which decreased during the therapeutic sessions.

Since the beginning, patient B selected specific pain descriptors and narrowly defined body areas (see Figure 2). During the therapeutic sessions, she selected similar descriptors of the MPQ Scale (mainly using sensory descriptors such as aching, tender, pulling, tiring, troublesome, pulsing or beating, and pressing or crushing). She indicated similar pain areas and intensity, thus suggesting a constant type of pain perception over time.

Figure 3 describes pain using MPQ and how it varied during sessions.

Both patients A and B show a general decrease in the indexes of PRI and NWC.

Note that patient A shows an increase in the PRI index at T9. This increase in pain rating does not correspond to a worsening perceived pain (PPI = 3) or the evaluative dimension (score = 0.8). Still, it may be a consequence of the scoring related to the sensory dimension, which may occasionally change due to the use of worse words to describe pain by the patient.

Focusing on the description of pain during the encounters led both patients to consider pain as changing in intensity and not necessarily being the same over hours and days.

Figure 4 reports McGill Pain Questionnaire (MPQ) scores in the three dimensions: Pain Sensory, Pain Affective, and Pain Evaluative, across INTEGRO measurement sessions (T0—pre-treatment evaluation; T2, T5, and T9—intermediate treatment evaluations; T12—final treatment evaluation).

Patient A shows increased sensorial component (score 5.6) and miscellaneous (score 3.0) at T9. Both patients show a reduction in scores on the sensory and affective subscales (patient A score in the sensory dimension is 2.0 and that in the affective dimension is 1.7; patient B scores are 2.3 and 0.5, respectively).

Patient A shows an increase in evaluative dimension (from a T2 score of 0.4 to a T12 score of 1), whereas patient B shows no variation over time.

Section b of Figure 4 highlights how the proportion of pain dimensions changes along the intervention. Both patients show a reduction and a redistribution of sensory and affective components at the end of the intervention.

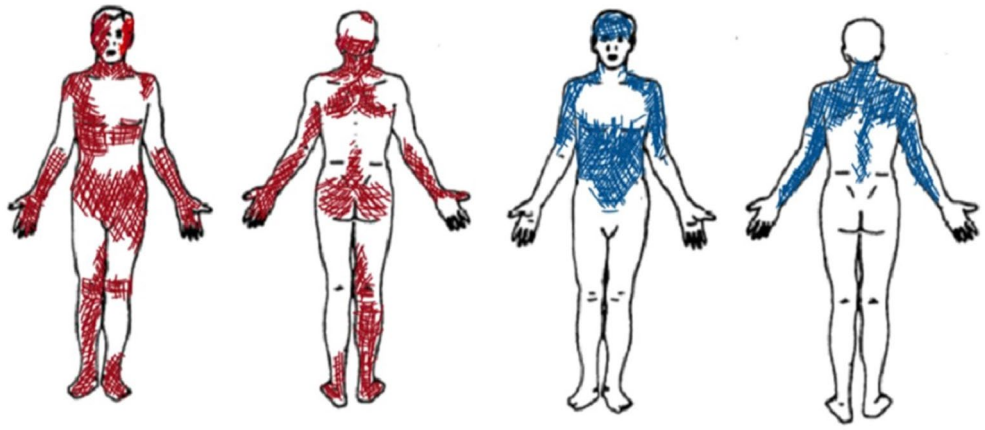

FIGURE 2
Graphic representation of pain localization as reported by Patient A (in red) and Patient B (in blue).

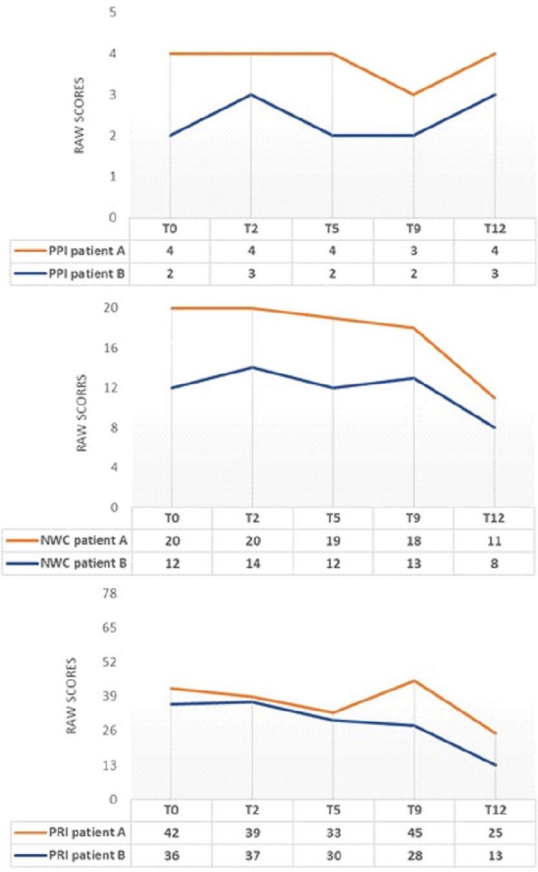

FIGURE 3
MPQ changes during INTEGRO evaluation sessions (T0-pre-treatment evaluation; T2, T5, T9-Intermediate treatment evaluations; T12-final treatment evaluation). PPI=Present Pain Intensity (Score range 0-5)is a numeric-verbal combination that indicates overall pain intensity rated on a 6- point Likert scale ranging from 'none'(0) to 'atrocious'(5); NWC=Number of Words Chosen (Score range 0–20), this index represents the number of words used to describe pain; PRI-Pain Rating Index (Score range 0–78),the score is based on position or order of rank in the set of words and describe a qualitative pain perception (55, 56).

3.2.2 Pre (T0)- and post (T13)-intervention assessment: fibromyalgia interference, pain intensity, perception of self-efficacy, and emotional regulation

Table 2 shows the results of clinical assessment at T0 and T13.

As for FM interference, both patients showed an improvement in the total score of FIQ (patient A ranged from 93.8 to 84; patient B ranged from 77.3 to 53) as well as for the Physical function subscale (patient A ranged from 28.3 to 28; patient B ranged from 21.3 to 16), Overall impact (patient A ranged from 20 to 18; patient B ranged from 11 to 0), and Symptoms (patient A ranged from 45.5 to 38; patient B ranged from 45 to 37). In patient B, the change at T13 in total score was high enough to result in a change in severity status from "severe disease" (defined as a score range of 64–82) to "moderate disease" (defined as a score range of 41–63) according to the scores reported by Salaffi et al. (14).

As for the intensity and impact of pain (BPI questionnaire) during the previous 24 h, a slight reduction in pain intensity in patient A emerged (from a score of 8.6 to 7.8), while the dimensions of emotional interference and work interference were stable. In patient B, there is a reduction in pain interference on both the emotional dimension (from a score of 7, indicating a severe degree of interference, to 4.7, indicating a moderate degree of interference) and work–life activities (from a score of 6, indicating a low–moderate degree of interference to 2, indicating a mild low degree of interference) after the intervention.

As for self-efficacy (PSEQ questionnaire), in patient B a relevant increased sense of self-efficacy in pain management after the intervention was evident (from a score of 17 to 45), while patient A showed only a slight increase (from a score of 9 to 11).

The Emotional Regulation (DERS questionnaire) Scale improved in patient A, as evidenced by a decline in total scores (from a score of 131 to 98) and the subscale capacity to accept emotional responses (Non-acceptance T0 score of 28; T13 score of 13), impulse control (Impulse T0 score of 27; T13 score of 17), access to emotion regulation strategies (Strategies T0 score of 28; T13 score of 22), and emotional clarity (Clarity T0 score of 20; T13 score of 16).

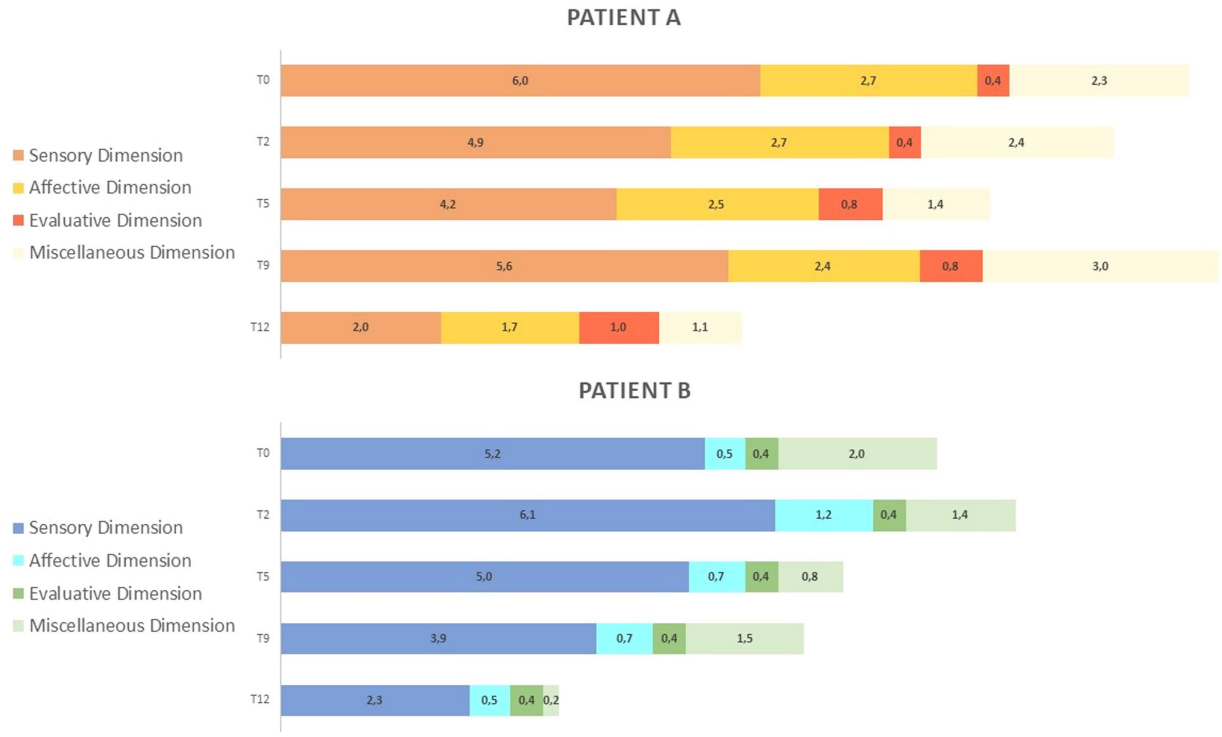

FIGURE 4
(A) MPQ scores in the three dimensions: Pain Sensory, Pain Affective, Pain Evaluative across INTEGRO measurement sessions (T0-pre-treatment evaluation; T2, T5, T9-intermediate treatment evaluations; T12-final treatment evaluations). The Sensory dimension (range 0-10) reports temporal, spatial, pressure, thermal, and other sensory properties of perceived pain. The Affective dimension (range 0-5) reflects tension, fear, emotional aspects of pain and automatic components. The Evaluative dimension (range 0–1) informs on the subjective overall intensity of experienced pain. (B) MPQ distribution over time (T0-pre treatment evaluation;T2,T5,T9- intermediate treatment evaluations; T12-final treatment evaluation) in dimensions: Pain sensory, Pain affective, Pain evaluative, Miscellaneous (range 0-4)which includes words that are often chosen but do not refer to any specific dimension.

Patient B reported a slight decrease in the Impulse subscale scores (Impulse T0 score of 22; T13 score of 18) and no significant changes in the other scores.

4 Discussion

Most protocols in the literature for the management of fibromyalgia syndrome tend to focus on standard cognitive behavioral therapies or individually implemented approaches in group sessions (64) The INTEGRO protocol integrates different strategies and techniques that draw on various methods. It also modulates the individual sessions' content based on the patients' experiences, making it possible to create a flexible intervention focused on the most problematic areas. It is also important to highlight how INTEGRO protocol integrates with treatments of a more medical nature and can easily be combined with rehabilitative interventions.

Examining each phase of the clinical INTEGRO protocol through the lens of its clinical application permitted us to comprehend (i) the relationship between various psychosocial factors and FM pain management and (ii) the process of change on which clinicians had to pay attention to consent the adaptation of INTEGRO intervention to clinical issues related to each patient's peculiarities.

Major FM patient characteristics were evident in both cases, representing an example of the wide range of symptoms and psychosocial mechanisms influencing pain and HrQoL (7, 8) in FM.

Patient A and patient B showed relevant differences in terms of:

1 Pain perception: more diffuse, with a peak during morning times and a higher affective component in patient A, and more selective, with a peak during evening times and with a prevalent avoiding attitude in patient B;
2 Psychosocial context: both were single, but patient A lived alone and could rely on a good network of friends, even if she did not share her pain-related worries; patient B lived with her parents and was very demanding of them;
3 Psychological functioning: patient A tended to blame herself when she was unable to gain her aims and tended to deny her needs; patient B tended to avoid feelings, paying attention mainly to bodily sensations and showing difficulties in mentalization processes;
4 Naïve explanation of illness: patient A tended to find a strong connection between emotional condition and physical response; patient B sought an explanation only through organic miens;
5 Coping strategies: patient A persisted with tasks beyond the perceived limit, iper-invested in managing pain, and tried to

10.3389/fmed.2024.1408693

TABLE 2 Results of clinical assessment Pre-treatment (T0) and post-treatment (T13).

	Patient A		Patient B	
	T0	T13	T0	T13
Revised Fibromyalgia Impact Questionnaire—FIQ				
Total score (score range 0–100)	93.8	84	77.3	53
Physical function (score range 0–30)	28.3	28	21.3	16
Overall impact (score range 0–20)	20	18	11	0
Symptoms (score range 0–50)	45.5	38	45	37
Brief Pain Inventory—BPI				
Pain intensity (score range 0–10)	8.6	7.8	6.4	7
Emotional interference (score range 0–10)	9.3	8.7	7	4.7
Work interference (score 0–10)	9.7	10	6	2
Pain Self-Efficacy Questionnaire—PSEQ				
Pain self-efficacy (score range 0–60)	9	11	17	45
Difficulties in Emotion Regulation Scale—DERS				
Total score (score range 33–165)	131	98	89	89
Non-acceptance (score range 6–30)	28	13	10	13
Goals (score range 5–25)	21	21	19	19
Impulse (score range 6–30)	27	17	22	18
Awareness (score range 3–15)	7	9	3	4
Strategies (score range 8–40)	28	22	25	24
Clarity (score range 5–25)	20	16	10	11

For each scale, minimum and maximum score variations are reported. For FIQ, lower scores indicate a lower impact of FM; for BPI and PSEQ, higher scores indicate higher interference of pain and perceived self-efficacy in pain management, respectively; for DERS, higher scores indicate more significant difficulties in emotional regulation.

prevent it by using several painkillers; patient B tried to use mainly control strategies, giving up when they were no longer effective with avoidance attitudes.

Despite these differences, after the INTEGRO intervention, both patients showed a reduction in the burden of FM as measured by the Revised Fibromyalgia Impact Questionnaire—FIQ, even if only patient B reported a significant change from the "severe disease" to the "moderate disease" category.

The improvement in health-related quality of life, despite the severity of physical disease, was related to the specific characteristics of each patient as has been evidenced by the combined use of many tools for assessing pain. This approach permitted a better investigation of the changes that have taken place during the intervention as well as a deeper analysis of the mechanisms on which to act to enhance positive outcomes.

Patient A started treatment with the idea that the onset and worsening of her symptoms were strongly interconnected with emotional stress and traumatic experiences, patient B tended to mainly trace the cause to previous medical conditions. Therefore, patient A showed much more sensitivity to all practices related to self-awareness, recognizing the progress obtained and feeling legitimated in her suffering. In contrast, patient B, as stated below, demonstrating a more significant improvement in perceived effectiveness in pain management, tended not to acknowledge these results, focusing more on the fatigue experienced to obtain them. Thus, these results suggest that the attribution of the causes of pain to mental or organic factors can primarily influence the predisposition to listen to one's internal states and recognize them. The more the attribution of the causes of pain is physical, the more the patient increases the search for external, rather than internal, resolution strategies, with a negative impact on the engagement in the treatment (e.g., in terms of carrying out homework foreseen in the protocol).

Although starting from different assumptions, both patients significantly improved their perceived self-efficacy in pain management and reduced the severity of the affective pain descriptors chosen during the sessions. In patient A, this was related to less need to use all categories to describe pain, selecting only those closely related to the present pain, suggesting a greater awareness of her bodily sensations. In patient B, this was related to achieving essential objectives in carrying out one's daily activities, reducing the tendency to avoid.

Another relevant mechanism to understand the change process regards the patient's subjective evaluation of pain and the role of affective and cognitive variables in pain perception (31, 65). Patients who perceive a lack of confidence in their pain management abilities also show negative expectations, a lower sense of agency, and poor investment in different coping strategies, which easily predisposes to a negative evaluation of one's level of functioning and emotional states characterized by anger, sadness, and fear. On the contrary, a more remarkable ability to regulate one's emotional states related to chronic pain promotes adaptation to the disease and using flexible and functional strategies for one's condition (25, 27). These observations are consistent with the results reported in the DERS Scale. Patient A showed an improvement in the subscales related to the tendency to experience negative secondary emotions or non-acceptance reactions in response to one's distress, the difficulties in maintaining control of one's behavior, the perception of having limited access to emotion regulation strategies, and lack of clarity to the emotions experienced. Still, as proposed in the protocol, experiential techniques made it possible to observe bodily signals with different attention (e.g., distinguishing, for example, whether what one feels is a painful stimulus or an expression of other experiences). In patient A, during the first sessions, the simple recognition of any internal change was confused with the preamble of something already experienced, such as pain, from which it was necessary to defend oneself and move away as quickly as possible (preventive avoidance strategies). In the last sessions, however, the patient considered how a physical signal did not

necessarily determine the onset of unmanageable pain, showing a welcoming and non-judgmental perception of her internal states. This allowed the patient to 'stay' with the pain at the proper emotional distance and evaluate which coping strategies might be most functional for her at that moment (shifting of attention—distraction, persistence in carrying out some activities—overdoing, even with a different rhythm—pacing, rest, and use of the drug). Patient B achieved essential goals in managing daily activities, for example, by proceeding with her activities with more functional rhythms and rest phases (pacing strategies). This was also possibly associated with a reduced tendency toward impulsivity in the DERS Scale. Patient B maintained the ability to recognize her internal states while maintaining difficulty in accepting her emotional reactions to exclude any form of vulnerability, including the experience of pain.

Finally, it is interesting to note how the intensity of pain in the last 24 h, measured in the two patients using the BPI Scale, did not show any clinically relevant variation in pre- and post-treatment due to high variability in the ongoing pain in FM patients. Therefore, it would be helpful to consider this variation on a larger timescale. Furthermore, this variability described by patients was perceived as an element capable of worsening their experience of uncertainty and anxiety about the future, a typical response to chronic medical conditions (66, 67). During the INTEGRO clinical protocol, great attention was paid to this aspect, helping patients consider how the prospect of significant variability between 1 day and another allowed them to accommodate even fewer "bad/ugly" moments to carry out different activities. Both patients achieved this objective due to using the MPQ Scale during the clinical sessions. A lower severity and intensity of sensory perceptions and reduced emotional involvement related to the pain experience allowed the two patients to coexist with the pain, reducing feelings of helplessness and the degree of interference with daily activities. This aligns with the reduction observed in the FIQ Scale and the increased sense of self-efficacy in pain management reported on the PSEQ Scale. Techniques focused on pain perception and, more generally, on interoceptive and exteroceptive stimuli enabled patients to learn to 'be' with their bodily sensations, perceiving them as less burdensome and catastrophic.

The clinical application of the protocol also allows some reflections regarding its limitations and future developments.

INTEGRO protocol seems promising, although the description of the two reported cases evidences how the potential effectiveness of the intervention depends on some specific characteristics of the patients, such as the subjectivity of pain evaluation. Thus, although considering all the topics covered in the clinical protocol, clinical psychologists must adapt the intervention to the patient's peculiarities. A good balance needs to be taken between the replicability of the intervention protocol and the need to modulate the number of psychotherapeutic sessions based on the history of the patient with FM, especially as many patients have a history of traumatic experiences (68), which often make body-based intervention more difficult.

INTEGRO intervention is provided only in person, which could be a restriction for patients who cannot move independently, for example, due to worsening pain symptoms. It might be helpful to provide the possibility of consultations through telematic platforms, which have proven useful and effective in breaking down barriers to accessibility and promoting positive outcomes, even in the case of chronic pain and fibromyalgia (39).

Our study aimed to show preliminary results on applying the INTEGRO intervention in the context of fibromyalgia. The high variability observed in the pain and psychological features of patients with fibromyalgia makes it challenging to generalize the findings reported in these cases to the larger clinical population. However, as regards future research, the INTEGRO intervention will be tested in a larger sample of patients with FM to explore its effectiveness and feasibility, and results will allow higher generalizability.

Moreover, applying the INTEGRO intervention on a larger clinical sample would allow us to adapt the intervention based on emerging needs and possible clinical subgroups, which could be categorized by type of pain, coping strategies employed, personality and clinical characteristics, the presence of trauma involving bodily dynamics, the stage of disease acceptance, and the patient's theories regarding the causes of the illness.

Another possible future evolution of INTEGRO protocol could be the promotion of maintenance groups focused not only on sharing experiences with other patients but also on maintaining the skills learned during the individual path, the integration of sessions dedicated to the creation of an information and educational space led by different specialists in the sector, open to caregivers and patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitato Etico per la Pratica Clinica Azienda Ospedaliera Universitaria Integrata. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

IP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. VD: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. EV: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. CP: Supervision, Writing – review & editing. MN: Investigation, Writing – review & editing. IL: Investigation, Supervision, Writing – review & editing. EP: Supervision, Writing – review & editing. VS: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing. LD: Conceptualization, Data curation, Funding acquisition,

Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The authors declare financial support was received for two scholar grants for Ilenia Pasini and Elisa Veneziani from the Italian Ministry of Research and University (MIUR) 5-year special funding to strengthen and enhance the excellence in research and teaching (CUP B31I18000240006 Department of Excellence—Dipartimento di Eccellenza). The publication fees were paid with the funding of PNRR Mission 4, Component 2, investment 1.1., financed by UE PRIN 2022 ricerca DEL PICCOLO "MobACT—Development, clinical efficacy and cost-effectiveness of a Mobile Acceptance and Commitment Therapy-based treatment for Chronic Primary Pain".

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Queiroz LP. Worldwide epidemiology of fibromyalgia topical collection on fibromyalgia. *Curr Pain Headache Rep*. (2013) 17:1–6. doi: 10.1007/S11916-013-0356-5/TABLES/2

2. Sarzi-Puttini P, Giorgi V, Marotto D, Atzeni F. Fibromyalgia: an update on clinical characteristics, aetiopathogenesis and treatment. *Nat Rev Rheumatol*. (2020) 16:645–60. doi: 10.1038/s41584-020-00506-w

3. Schweiger V, Perini G, Del Piccolo L, Perlini C, Donisi V, Gottin L, et al. Bipolar Spectrum symptoms in patients with fibromyalgia: a dimensional psychometric evaluation of 120 patients. *Int J Environ Res Public Health*. (2022) 19:16395. doi: 10.3390/IJERPH192416395

4. Bennett RM, Jones KD, Aebischer JH, St John AW, Friend R. Which symptoms best distinguish fibromyalgia patients from those with other chronic pain disorders? *J Eval Clin Pract*. (2022) 28:225–34. doi: 10.1111/JEP.13615

5. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. *Nat Rev Rheumatol*. (2011) 7:518–27. doi: 10.1038/nrrheum.2011.98

6. Mease P. Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment. *J Rheumatol Suppl*. (2005) 75:6–21.

7. Fors EA, Landmark T, Bakke Ø. Contextual and time dependent pain in fibromyalgia: an explorative study. *BMC Res Notes*. (2012) 5:644. doi: 10.1186/1756-0500-5-644

8. Martínez MP, Sánchez AI, Prados G, Lami MJ, Villar B, Miró E. Fibromyalgia as a heterogeneous condition: subgroups of patients based on physical symptoms and cognitive-affective variables related to pain. *Span J Psychol*. (2021) 24:e33. doi: 10.1017/SJP.2021.30

9. Drozd M, Marzęda M, Blicharz A, Czarnota J, Piecewicz-Szczęsna H. Unclear etiology and current hypotheses of the pathogenesis of fibromyalgia. *J Educ Health Sport*. (2020) 10:338–44. doi: 10.12775/JEHS.2020.10.09.038

10. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum*. (2007) 36:339–56. doi: 10.1016/J.SEMARTHRIT.2006.12.009

11. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience*. (2016) 338:114–29. doi: 10.1016/J.NEUROSCIENCE.2016.06.006

12. Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. *Arthritis Res Ther*. (2007) 8:2094. doi: 10.1186/AR2094

13. Martínez-Lavín M. Fibromyalgia and small fiber neuropathy: the plot thickens! *Clin Rheumatol*. (2018) 37:3167–71. doi: 10.1007/s10067-018-4300-2

14. Salaffi F, Di Carlo M, Bazzichi L, Atzeni F, Govoni M, Biasi G, et al. Definition of fibromyalgia severity: findings from a cross-sectional survey of 2339 Italian patients. *Rheumatology*. (2021) 60:728–36. doi: 10.1093/RHEUMATOLOGY/KEAA355

15. Black LL, Black WR, Chadwick A, Christofferson JL, Katz H, Kragenbrink M. Investigation of patients' understanding of fibromyalgia: results from an online qualitative survey. *Patient Educ Couns*. (2024) 122:108156. doi: 10.1016/J.PEC.2024.108156

16. Haugli L, Strand E, Finset A. How do patients with rheumatic disease experience their relationship with their doctors?: a qualitative study of experiences of stress and support in the doctor–patient relationship. *Patient Educ Couns*. (2004) 52:169–74. doi: 10.1016/S0738-3991(03)00023-5

17. Galvez-Sánchez CM, Duschek S, Reyes GA, Paso D. Psychological impact of fibromyalgia: current perspectives. *Psychol Res Behav Manag*. (2019) 12:117–27. doi: 10.2147/PRBM.S178240

18. Armentor JL. Living with a contested, stigmatized illness: experiences of managing relationships among women with fibromyalgia. *Qual Health Res*. (2017) 27:462–73. doi: 10.1177/1049732315620160

19. Fernandez-Feijoo F, Samartin-Veiga N, Carrillo-de-la-Peña MT. Quality of life in patients with fibromyalgia: contributions of disease symptoms, lifestyle and multi-medication. *Front Psychol*. (2022) 13:4405. doi: 10.3389/FPSYG.2022.924405

20. Pinto AM, Geenen R, Wager TD, Lumley MA, Häuser W, Kosek E, et al. Emotion regulation and the salience network: a hypothetical integrative model of fibromyalgia. *Nat Rev Rheumatol*. (2022) 19:44–60. doi: 10.1038/s41584-022-00873-6

21. Galvez-Sánchez CM, Montoro CI, Duschek S, Reyes del Paso GA. Depression and trait-anxiety mediate the influence of clinical pain on health-related quality of life in fibromyalgia. *J Affect Disord*. (2020) 265:486–95. doi: 10.1016/J.JAD.2020.01.129

22. Trucharte A, Leon L, Castillo-Parra G, Magán I, Freites D, Redondo M. Emotional regulation processes: influence on pain and disability in fibromyalgia patients. *Clin Exp Rheumatol*. (2020) 38:40–6.

23. Kurtze N, Svebak S. Fatigue and patterns of pain in fibromyalgia: correlations with anxiety, depression and co-morbidity in a female county sample. *Br J Med Psychol*. (2001) 74:523–37. doi: 10.1348/000711201161163

24. Sánchez AI, Martínez MP, Miró E, Medina A. Predictors of the pain perception and self-efficacy for pain control in patients with fibromyalgia. *Span J Psychol*. (2011) 14:366–73. doi: 10.5209/REV_SJOP.2011.V14.N1.33

25. Wierenga KL, Lehto RH, Given B. Emotion regulation in chronic disease populations: an integrative review. *Res Theory Nurs Pract*. (2017) 31:247–71. doi: 10.1891/1541-6577.31.3.247

26. Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. *J Psychopathol Behav Assess*. (2004) 26:41–54. doi: 10.1023/B:JOBA.0000007455.08539.94

27. de Ridder D, Geenen R, Kuijer R, van Middendorp H. Psychological adjustment to chronic disease. *Lancet*. (2008) 372:246–55. doi: 10.1016/S0140-6736(08)61078-8

28. Borg C, Chouchou F, Dayot-Gorlero J, Zimmerman P, Maudoux D, Laurent B, et al. Pain and emotion as predictive factors of interoception in fibromyalgia. *J Pain Res*. (2018) 11:823–35. doi: 10.2147/JPR.S152012

29. Valenzuela-Moguillansky C, Reyes-Reyes A, Gaete MI. Exteroceptive and interoceptive body-self awareness in fibromyalgia patients. *Front Hum Neurosci*. (2017) 11:117. doi: 10.3389/FNHUM.2017.00117/FULL

30. Thieme K, Turk DC, Flor H. Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. *Psychosom Med*. (2004) 66:837–44. doi: 10.1097/01.PSY.0000146329.63158.40

31. Palomino RA, Nicassio PM, Greenberg MA, Medina EP. Helplessness and loss as mediators between pain and depressive symptoms in fibromyalgia. *Pain*. (2007) 129:185–94. doi: 10.1016/J.PAIN.2006.12.026

32. Sardá J, Nicholas MK, Asghari A, Pimenta CAM. The contribution of self-efficacy and depression to disability and work status in chronic pain patients: a comparison between Australian and Brazilian samples. *Eur J Pain*. (2009) 13:189–95. doi: 10.1016/J.EJPAIN.2008.03.008

33. Racine M, Galán S, De La Vega R, Pires CT, Solé E, Nielson WR, et al. Pain-related activity management patterns and function in patients with fibromyalgia syndrome. *Clin J Pain*. (2018) 34:122–9. doi: 10.1097/AJP.0000000000000526

34. Karsdorp PA, Vlaeyen JWS. Active avoidance but not activity pacing is associated with disability in fibromyalgia. *Pain*. (2009) 147:29–35. doi: 10.1016/J.PAIN.2009.07.019

35. Meireles SA, Antero DC, Kulczycki MM, Skare TL. Prevalence of falls in fibromyalgia patients. *Acta Ortop Bras*. (2014) 22:163–6. doi: 10.1590/1413-78522014220300386

36. Clare P, Stanley R. The psychological management of chronic pain: A treatment manual. Berlin: Springer Pub. Co. (1996). 286 p.

37. Devine DP, Spanos NP. Effectiveness of maximally different cognitive strategies and expectancy in attenuation of reported pain. *J Pers Soc Psychol*. (1990) 58:672–8. doi: 10.1037/0022-3514.58.4.672

38. Garcia-Campayo J, Pascual A, Alda M, Gonzalez Ramirez MT. Coping with fibromialgia: usefulness of the chronic pain coping Inventory-42. *Pain*. (2007) 132:S68–76. doi: 10.1016/J.PAIN.2007.02.013

39. Donisi V, De Lucia A, Pasini I, Gandolfi M, Schweiger V, Del Piccolo L, et al. E-health interventions targeting pain-related psychological variables in fibromyalgia: a systematic review. *Healthcare*. (2023) 11:1845. doi: 10.3390/HEALTHCARE11131845

40. Thieme K, Turk D. Leitlinien und EULAR-Empfehlungen für die Behandlung der Fibromyalgie. *Schmerz*. (2017) 31:170–8. doi: 10.1007/s00482-016-0179-5

41. Ariani A, Bazzichi L, Puttini PS, Salaffi F, Manara M, Prevete I, et al. The Italian Society for Rheumatology clinical practice guidelines for the diagnosis and management of fibromyalgia. Best practices based on current scientific evidence. *Reumatismo*. (2021) 73:89–105. doi: 10.4081/reumatismo.2021.1362

42. Luciano JV, Neblett R, Peñacoba C, Suso-Ribera C, McCracken LM. The contribution of the psychologist in the assessment and treatment of fibromyalgia. *Curr Treatm Opt Rheumatol*. (2023) 9:11–31. doi: 10.1007/S40674-023-00200-4

43. Häuser W, Arnold B, Eich W, Felde E, Flügge C, Henningsen P, et al. Management of fibromyalgia syndrome – an interdisciplinary evidence-based guideline. GMS German. *Med Sci*. (2008) 6:Doc14. doi: 10.3238/arztebl.2009.0383

44. Donisi V, Mazzi MA, Gandolfi M, Deledda G, Marchioretto F, Battista S, et al. Exploring emotional distress, psychological traits and attitudes in patients with chronic migraine undergoing OnabotulinumtoxinA prophylaxis versus withdrawal treatment. *Toxins*. (2020) 12:577. doi: 10.3390/TOXINS12090577

45. Bernardy K, Füber N, Köllner V, Häuser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome — a systematic review and Metaanalysis of randomized controlled trials. *J Rheumatol*. (2010) 37:1991–2005. doi: 10.3899/JRHEUM.100104

46. Bernardy K, Klose P, Welsch P, Häuser W. Efficacy, acceptability and safety of cognitive behavioural therapies in fibromyalgia syndrome – a systematic review and meta-analysis of randomized controlled trials. *Eur J Pain*. (2018) 22:242–60. doi: 10.1002/EJP.1121

47. Luciano JV, Guallar JA, Aguado J, López-Del-Hoyo Y, Olivan B, Magallón R, et al. Effectiveness of group acceptance and commitment therapy for fibromyalgia: a 6-month randomized controlled trial (EFFIGACT study). *Pain*. (2014) 155:693–702. doi: 10.1016/J.PAIN.2013.12.029

48. Weisfeld CC, Dunleavy K. Strategies for managing chronic pain, chronic PTSD, and comorbidities: reflections on a case study documented over ten years. *J Clin Psychol Med Settings*. (2021) 28:78–89. doi: 10.1007/S10880-020-09741-5

49. Islam Z, D'Silva A, Raman M, Nasser Y. The role of mind body interventions in the treatment of irritable bowel syndrome and fibromyalgia. *Front Psych*. (2022) 13:1076763. doi: 10.3389/FPSYT.2022.1076763

50. Courtois I, Cools F, Calsius J. Effectiveness of body awareness interventions in fibromyalgia and chronic fatigue syndrome: a systematic review and meta-analysis. *J Bodyw Mov Ther*. (2015) 19:35–56. doi: 10.1016/J.JBMT.2014.04.003

51. Pasini I, Perlini C, Donisi V, Mason A, Schweiger V, Secchettin E, et al. "INTEGRO INTEGRated psychotherapeutic InterventiOn" on the Management of Chronic Pain in patients with fibromyalgia: The role of the therapeutic relationship. *Int J Environ Res Public Health*. (2023) 20:3973. doi: 10.3390/ijerph20053973

52. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. (2016) 46:319–29. doi: 10.1016/J.SEMARTHRIT.2016.08.012

53. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The revised fibromyalgia impact questionnaire (FIQR): validation and psychometric properties. *Arthritis Res Ther*. (2009) 11:R120. doi: 10.1186/AR2783

54. Salaffi F, Franchignoni F, Giordano A, Ciapetti A, Sarzi-Puttini P, Ottonello M. Psychometric characteristics of the italian version of the revised fibromyalgia impact questionnaire using classical test theory and rasch analysis. *Clin Exp Rheumatol*. (2013) 72:A714.3–A714. doi: 10.1136/annrheumdis-2013-eular.2112

55. Melzack R. The McGill pain questionnaire: major properties and scoring methods. *Pain*. (1975) 1:277–99. doi: 10.1016/0304-3959(75)90044-5

56. Maiani G, Sanavio E. Semantics of pain in Italy: the Italian version of the McGill pain questionnaire. *Pain*. (1985) 22:399–405. doi: 10.1016/0304-3959(85)90045-4

57. Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin brief pain questionnaire to assess pain in cancer and other diseases. *Pain*. (1983) 17:197–210. doi: 10.1016/0304-3959(83)90143-4

58. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap*. (1994) 23:129–38.

59. Caraceni A, Mendoza TR, Mencaglia E, Baratella C, Edwards K, Forjaz MJ, et al. A validation study of an Italian version of the brief pain inventory (breve Questionario per la Valutazione del Dolore). *Pain*. (1996) 65:87–92. doi: 10.1016/0304-3959(95)00156-5

60. Bonezzi C, Nava A, Barbieri M, Bettaglio R, Demartini L, Miotti D, et al. Validazione della versione italiana del Brief Pain Inventory nei pazienti con dolore cronico. *Minerva Anestesiol*. (2002) 68:607–11.

61. Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. *Eur J Pain*. (2007) 11:153–63. doi: 10.1016/J.EJPAIN.2005.12.008

62. Chiarotto A, Vanti C, Ostelo RW, Ferrari S, Tedesco G, Rocca B, et al. The pain self-efficacy questionnaire: cross-cultural adaptation into Italian and assessment of its measurement properties. *Pain Pract*. (2015) 15:738–47. doi: 10.1111/PAPR.12242

63. Sighinolfi C, Pala AN, Chiri L, Marchetti I, Sica C. *Difficulties in Emotion Regulation Scale (DERS): traduzione e adattamento italiano*. (2010).

64. Albajes K, Moix J. Psychological interventions in fibromyalgia: an updated systematic review. Mediterranean. *J Clin Psychol*. (2021) 9:2759. doi: 10.6092/2282-1619/MJCP-2759

65. Keefe FJ, Rumble ME, Scipio CD, Giordano LA, Perri LCM. Psychological aspects of persistent pain: current state of the science. *J Pain*. (2004) 5:195–211. doi: 10.1016/J.JPAIN.2004.02.576

66. Wright LJ, Afari N, Zautra A. The illness uncertainty concept: a review. *Curr Pain Headache Rep*. (2009) 13:133–8. doi: 10.1007/S11916-009-0023-Z

67. McInnis OA, Matheson K, Anisman H. Living with the unexplained: coping, distress, and depression among women with chronic fatigue syndrome and/or fibromyalgia compared to an autoimmune disorder. *Anxiety Stress Coping*. (2014) 27:601–18. doi: 10.1080/10615806.2014.888060

68. Romeo A, Tesio V, Ghiggia A, Di Tella M, Geminiani GC, Farina B, et al. Traumatic experiences and somatoform dissociation in women with fibromyalgia. *Psychol Trauma*. (2022) 14:116–23. doi: 10.1037/TRA0000907

69. Joann D, Lundgren T. Oltre il dolore cronico: vivere in modo pieno e vitale. Milan, Italy: Franco Angeli (2014).

70. Ogden P, Fisher J. Psicoterapia sensomotoria. Raffaello Cortina: Interventi per il Trauma e l'attaccamento (2016).

71. Marchi L, Blasutti V. *Terapia cognitivo-comportamentale per la fibromialgia: Un trattamento psicologico integrato per la gestione del dolore cronico. edizione digitale* (2021).

72. Derogatis LR. SCL-90-R: Symptom Checklist-90-R: Administration, scoring, and procedures manual. Minneapolis: National Computer Systems. Inc. (1994).

73. Sarno I, Preti E, Prunas A, Madeddu F. *SCL-90-R symptom Checklist-90-R Adattamento italiano*. (2011).

74. Prunas A, Sarno I, Preti E, Madeddu F, Perugini M. Psychometric properties of the Italian version of the SCL-90-R: a study on a large community sample. *Eur Psychiatry*. (2012) 27:591–7. doi: 10.1016/j.eurpsy.2010.12.006

75. Sperling MB, Berman WH. Attachment in adults: Clinical and developmental perspectives. New York, USA: Guilford Press (1994).

76. Fossati A, Feeney JA, Grazioli F, Borroni S, Acquarini E, Maffei C. L'Attachment style questionnaire (ASQ) Di Feeney, Noller E Hanrahan. Milan, Italy: Raffaello Cortina (2007).

77. Nijenhuis ERS, Van der Hart O, Kruger K. The psychometric characteristics of the traumatic experiences checklist (TEC): first findings among psychiatric outpatients. *Clin Psychol Psychother*. (2002) 9:200–10. doi: 10.1002/cpp.332

78. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. *Assessment*. (2006) 13:27–45. doi: 10.1177/1073191105283504

79. Giovannini C, Giromini L, Bonalume L, Tagini A, Lang M, Amadei G. The Italian five facet mindfulness questionnaire: a contribution to its validity and reliability. *J Psychopathol Behav Assess*. (2014) 36:415–23. doi: 10.1007/s10862-013-9403-0

80. Messina I, Sambin M, Palmieri A. Measuring therapeutic empathy in a clinical context: validating the Italian version of the empathic understanding of relationship inventory. *TPM Test Psychometr Methodol Appl Psychol*. (2013) 20:1–11.

81. Barrett-Lennard G. The relationship inventory now: issues and advances in theory, method and use In: LS Greenberg and WM Pinsof, editors. The psychotherapeutic process: A research handbook. New York, USA: Guilford Press (1986)

82. Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the working alliance inventory. *Psychother Res*. (2006) 16:12–25. doi: 10.1080/10503300500352500

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