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Movement-evoked pain is not associated with pain at rest or physical function in knee osteoarthritis

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Abstract

Introduction: Knee Osteoarthritis (KOA) is mainly characterized by pain. The assessment of KOA-related pain frequently focuses on different constructs subject to sources of bias or drawbacks, as the classical Pain at Rest (PAR). Movement-evoked pain (MEP), recently defined as 'pain during walking', emerges as a differential concept, since PAR and MEP are driven by different underlying mechanisms. Given the novelty of the MEP approach, its association with PAR or with different performance-based tests has not been studied in KOA yet.

Materials and Methods: A cross sectional study was conducted. PAR was measured, alongside the performance of four mobility tests and their corresponding MEP: Timed Up and Go Test, 10-metre Walk Test, 2-Minute Walk Test, and 6-Minute Walk Test. Association and agreement were explored for MEP versus PAR, while the correlation of the tests versus each corresponding MEP-measure was assessed.

Results: Neither association nor agreement were found in the duality MEP versus PAR. Also, the lack of association between the performance of a mobility test and the perceived level of pain during the development of the test was stated.

Conclusion: Movement-evoked pain is neither related to pain at rest nor to functional performance in subjects affected by knee osteoarthritis. The results from our study suggest that MEP and pain at rest measure and refer to different constructs in knee osteoarthritis. The implementation of MEP as an outcome in exercise-therapy could enhance the tracking of results, as well as the development of tailored interventions under different conditions.

Significance: This research elucidates the relevance of MEP, recently defined as 'pain during walking', through the analysis of its association with PAR and with functional performance (measured through four mobility tests) in knee osteoarthritis. The results from our study highlight the absence of either association or agreement between MEP and PAR, fact that supports and endorses the idea that both concepts measure and refer to different constructs in knee osteoarthritis.

1 | INTRODUCTION

Knee Osteoarthritis (KOA) is a common progressive disease mainly characterized by chronic pain and functional disability (Hunter & Bierma-Zeinstra, 2019), with a global prevalence of 595,000,000 (95% CI: 535,000,000–656,000,000) cases worldwide, which involves roughly 7.6% (95% CI: 6.8%–8.4%) of the global population, and an increase of 132.2% (95% CI: 130.3%–134.1%) in total cases since 1990 (GBD 2021 Osteoarthritis Collaborators, 2023).

The adequate tracking of symptoms in KOA is usually complex due to unstable symptoms (Previtali et al., 2020). Pain is the most common symptom in KOA, and its assessment is therefore a key-point in clinical practice (Lespasio et al., 2017). The assessment of KOA-related pain frequently focuses in either spontaneous pain, pain at rest or pain recalled through questionnaires (Davis et al., 2022; Litcher-Kelly et al., 2007). For instance, the Western-Ontario Scale and the McMaster Universities Arthritis Index (WOMAC) has been commonly used to assess the main characteristics of the pathology itself, such as pain, stiffness, and functionality (Bellamy et al., 1988): while some of its items from the WOMAC instrument provide an insight on the assessment of pain under different conditions, the perceived level of pain is subject to recall bias between the eventual mean level of pain instantly reported and the level reported with a retrospective assessment (Previtali et al., 2022).

Movement-evoked pain (MEP) was initially described as pain reported during movement or physical activity (Graven-Nielsen & Arendt-Nielsen, 2010) of the activation of silent nociceptors that respond to joint movement or other types of stimuli that are usually not painful. More recently, it has been defined as 'pain during walking' (Fullwood et al., 2021). MEP is often initiated in response to tissue damage through peripheral mechanisms of inflammation that can drive sensitization via maladaptive changes in the response properties of peripheral and/or central neurons (Corbett et al., 2019). The distinction between MEP and other concepts of pain (as spontaneous pain or pain at rest) is of paramount importance, since the existing literature suggests that both are driven by different underlying mechanisms (Corbett et al., 2019). Different tests for the assessment of MEP in specific conditions (such as chronic low back pain) are being developed (Simon et al., 2023), and its importance as an emerging measure in the assessment in KOA is therefore capital, as it has already been highlighted elsewhere (Booker et al., 2019). Despite having been studied in different conditions (Fullwood et al., 2021), the specific association between MEP and pain at rest (PAR) has not been studied in the framework of KOA yet: Sayers et al. explored both constructs after knee replacements (Sayers et al., 2016), highlighting the importance of future work to explore the mechanisms underlying MEP and PAR. In the field of KOA, solely Overton et al. have recently examined the association between MEP (during the 6-Minute Walk Test, 6MWT) and self-reported pain (through different instruments considering self-reported pain with movement, spontaneous pain, or PAR), stating an existing association between both constructs (Overton et al., 2023).

Pain influences the physical performance of different mobility tests, showing an important impact on variables as gait speed (Hutchison et al., 2023) and even the gait pattern (Ro et al., 2019). Pain has even been described as a predictor of walking capacity in obese adults with KOA (Yázigi et al., 2018). The assessment of functional mobility measures involving walking is therefore of paramount importance and can be channelled through different tests, such as the 10-meter Walk Test (10mWT), the Timed Up and Go test (TUGT), or the 6- and 2-Minute Walk Test (2MWT and 6MWT, respectively) (Gacto-Sánchez et al., 2023; Lee et al., 2022). The association between classical pain measures (i.e. pain during the past week, pain at rest, self-reported pain through questionnaires, etc.) and functional mobility performance has been thoroughly explored and described in different conditions (Ahmed et al., 2022; Dailey et al., 2016; McBeth et al., 2010; Serpas et al., 2022).

In the field of KOA, the association of severe MEP and low physical functional performance has been linked to less-favourable psychological characteristics in community-dwelling individuals at risk for KOA (Cruz-Almeida et al., 2017), but solely Overton et al., as in the duality 'MEP/self-reported pain' have evaluated the association between MEP (during the performance of the 6MWT) and functional performance based on walking activities (through the 6MTW itself), stating not only an existing association between both measures but, moreover, the ability of MEP to predict functional outcomes and even pain in patients with KOA (Overton et al., 2023). Notwithstanding the aforementioned, Overton et al. focused on a sole MEP measure (i.e. pain during the 6MWT), and only one performance-based test involving walking (6MWT) (Overton et al., 2023).

For all the above mentioned, the objectives of the current study were (1) to explore and describe the association between self-reported pain at rest and movement-evoked pain and (2) to assess the association between different performance-based tests and their corresponding levels of movement-evoked pain in patients affected by knee osteoarthritis.

2 | METHODS

2.1 | Participants

A cross-sectional study was conducted among a sample of patients with KOA, from the Morales Meseguer University Hospital (Murcia, Spain) within the period between January 2022 and March 2023. Potential participants were preliminarily screened from the appointment lists of the departments of Rehabilitation, Traumatology and Rheumatology, whenever they had the diagnosis of knee osteoarthritis, according to the following eligibility criteria.

2.2 | Inclusion criteria

Adults over 50 years of age with a radiographic diagnosis of knee osteoarthritis, since plain radiography (both knees, weight-bearing, semi-flexed—medial tibial plateau—view, plus a lateral and skyline view) is the current 'gold standard' for the morphological assessment of KOA (Zhang et al., 2010). Also, compliance with the diagnostic criteria for KOA stated by the American College of Rheumatology was required: presence of morning stiffness under 30 min of duration; absence of hyperthermia upon palpation in the joint; presence of alteration of the bone image and presence of crepitus under gravity (Altman et al., 1986).

2.3 | Exclusion criteria

Patients were excluded if they met any of the following criteria: patients potentially providing low-quality or biased information discriminated by the Mini-Mental State Examination (scores below 24 points); severe hearing, visual or sensory impairment or comorbidities preventing the correct completion of the questionnaires and/or mobility activities; patients who had undergone knee replacement surgery on the contralateral knee; patients who had received invasive interventions (infiltration, blockages, etc.…) in the last 6 weeks; pain due to tendinopathies, knee fracture, low back pain radiating to the knee, or fibromyalgia; Body Mass Index above 45; severe heart disease preventing exercise or unstable pulmonary conditions.

The research plan was submitted to and approved by the Ethics Committee of the University of Murcia (Murcia, Spain) (3536/2021) and the Committee of the Morales Meseguer University Hospital (Murcia, Spain) (ENS 14/21). All patients received the corresponding Information Sheet and provided written Informed Consent prior to the study onset.

2.4 | Procedure

Sociodemographic and clinical variables were collected by means of self- or hetero-administered questionnaires and simple interview. Sociodemographic variables were age, weight, height, professional situation, and level of studies. Clinical variables included duration of symptoms, degree of KOA (Kellgren-Lawrence grading scale), pain at rest—PAR—(Visual Analogue Scale, VAS), use of assistive devices for walking, and performance and related-MEP of the following functional mobility tests involving walking: TUGT, 10mWT, 2MWT and 6 MWT. PAR was measured, in the same line than some of the items from the Brief Pain Inventory or the KOOS, as the pain on average that the subject had experienced at rest in the week prior to the assessment (i.e. in the last 7 days) (Overton et al., 2023). As for MEP, the task was performed and, right after the completion of the aforementioned task, the subject was requested to score the pain suffered during the development of the task, according to the definition by Corbett et al. (2019).

Functional mobility tests were performed sequentially, from the lighter to the heavier (i.e. TUGT, 10mWT, 2MTW, and 6MWT) with the aim minimizing the potential effects of fatigue and pain that could occur due to high loads or demands of the 6MWT, basically (Amatachaya et al., 2014). The four performance tests were administered and registered by the same investigator (JAL-M), to avoid inter-rater bias, as suggested elsewhere (Goldman et al., 2008).

2.4.1 | Timed Up and Go Test (TUGT)

Patients are requested to stand up (not using their arms) from a standard chair, walk until a mark on the floor place at 3 m, turn around, and walk back to sit down in the chair again. Routine walking aids, if needed, is permitted. The time to complete the task is the outcome measure of this test (Alghadir et al., 2015).

2.4.2 | 10-meter Walk Test (10mWT)

The time (in seconds) to walk the middle 10-m section of a 15-m walkway is registered, commencing from a dynamic starting: timing starts when the participant's first foot crosses the 2-m mark and stops when the first foot crosses the 12-m mark, though the participant continues to walk the remaining 3 m to the 15-m mark (Cheng et al., 2020). No encouragement is given during the test. Walking speed is subsequently calculated (10 m/time spent in seconds).

2.4.3 | 2-Minute Walk Test (2MWT) and 6-Minute Walk Test (6MWT)

Patients walks, at maximal effort, back and forth, in a 30-m hallway turning around cones, with the possibility of using their habitual assistive devices, as described in the guidelines of the test, during 2 or 6 min, depending on the test. During the test, the investigator walks alongside the patient to ensure his/her safety, as well as to provide him/her with verbal encouragement at 1-min intervals. The distance covered at the end of the 2- or the 6-min period is recorded (ATS Statement, 2002). Both tests were separated by a 30-min rest period, as suggested by Gijbels et al. (2011).

MEP was measured through VAS and operationalized by requesting the patient to provide the level of pain experienced concurrently during the test, almost at the end of his/her performance (Fullwood et al., 2021).

2.4.4 | Statistical analyses

Data were assessed for normality through the Kolmogorov–Smirnov test, since the final sample size corresponded to 59 patients (Mishra et al., 2019).

Descriptive statistics were used to characterize the sample, through mean ± standard deviations, or frequencies (percentages), based on the quantitative or qualitative nature of each variable.

Pearson or Spearman correlations (depending on the normality of data) were run to assess the association between PAR (baseline measure) and MEP pain stemming from each functional performance test. A Bland–Altman plot was built to evaluate the agreement between PAR and MEP pain from the 6MWT, since it is the closest potential comparison to a previously existing reference in the scientific literature (Overton et al., 2023).

Pearson or Spearman correlations were also used to assess the association between each performance measure and their corresponding MEP. In the case of the TUGT, since the variable was categorized (below 10 s; between 10 and 20 s; beyond 20 s), the corresponding degree of correlation was assessed through the obtention of the Kendall rank correlation coefficient.

All analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (Armonk, NY, USA: IBM Corp; 2016), with a *p*-level of significance set at $p < 0.05$.

Post-hoc power of the study, considering the sample size and the effect sizes obtained, was subsequently calculated through G*Power (G*Power 3.1.9.7 for Windows, Heinrich-Heine-Universität, Düsseldorf, Germany).

3 | RESULTS

A total of 82 subjects were initially approached: among them, 5 declined to participate, while 16 did not meet eligibility criteria and they were subsequently excluded. The reasons for exclusion were not fully meeting inclusion criteria (9 subjects), fibromyalgia (2), Mini-Mental State Examination below 24 points (2), total knee replacement on the contralateral knee (2), and knee infiltrations in the 6-week period prior to the study onset (1). Once the study scheduled, two participants dropped out due to transportation issues. A total of 59 participants completed the study. Sociodemographic and clinical characteristics of the sample are displayed in Table 1. Around 75% of the sample was composed by women, and mean age was 68.58 ± 8.43 years. Patients had experienced symptoms for around 48 months, and roughly 15% of the sample needed assistive devices for walking. The mean VAS pain at rest was 6.59 ± 2.09, while the mean values of the MEP for the four walking performance tests were included in a 2.24-to-3.37 range.

Data were tested for normality through the Kolmogorov–Smirnov test, and the subsequent parametric or non-parametric approaches were therefore adopted. Table 2 displays the different correlation coefficients alongside the corresponding *p*-values of the different correlations tested. All the coefficients stem from Spearman Rho correlations, except for the MEP on the TUGT (since the results were categorized, Kendall's Tau correlation was implemented). All MEP-based measures correlated among them, with coefficients ranging from 0.577 to 0.921, in a moderate-strong to very strong magnitude of association (Schober et al., 2018), with *p*-values below 0.001. Concerning baseline pain, differences were statistically significant solely for its correlation with two of the measures but, moreover, baseline pain correlated with MEP-based measures in a 0.233-to-0.307 range, which entails a very weak correlation (Schober et al., 2018).

Figure 1 displays the Bland–Altman plot used to evaluate the agreement among two of the measures approached: PAR versus 6MWT-MEP. The mean difference was 3.12 ± 3.03. The corresponding 95% CI Limits of

TABLE 1 Baseline sociodemographic and clinical characteristics ($n = 59$).

Variables	Mean ± SD or *N* (%)
Sociodemographic variables	
Age (years)	68.58 ± 8.43
Gender	
Male	14 (23.70)
Female	45 (76.30)
Weight (kg)	77.52 ± 12.31
Height (cm)	162.05 ± 8.49
Body mass index (kg/m^2)	29.53 ± 4.23
Labour situation	
Active	12 (20.30)
Sick leave	6 (10.20)
Housewife/Househusband	5 (8.50)
Retired	36 (61.00)
Level of studies	
No formal education	6 (10.20)
Primary studies	23 (39.00)
Secondary studies	15 (25.40)
Higher education	15 (25.40)
Clinical variables	
Duration of symptoms (months)	48.51 ± 51.91
Kellgren–Lawrence degree	
I	1 (1.69)
II	28 (47.45)
III	27 (45.76)
IV	3 (5.08)
Pain at rest (baseline) (VAS)	6.59 ± 2.09
Assistive devices for walking	
No	50 (84.70)
Yes	9 (15.30)
Timed up and go test	
<10 s	2 (3.40)
10–20 s	46 (78.00)
>20 s	11 (18.60)
MEP timed up and go test (VAS)	2.24 ± 2.52
10-metre walk test (m/s)	0.59 ± 0.16
MEP 10-metre walk test (VAS)	2.42 ± 2.62
2-minute walk test (m)	83.64 ± 18.84
MEP 2-minute walk test (VAS)	2.84 ± 2.57
6-minute walk test	241.65 ± 56.61
MEP 6-minute walk test (VAS)	3.37 ± 2.91

Abbreviations: m, meters; MEP, movement-evoked pain; *N*, number; s, seconds; SD, standard deviation; VAS, Visual Analogue Scale.

Agreement (LoA) were calculated according to the formula 'Mean ± 1.96*SD', subsequently providing values of −2.81 and 9.05 for the lower and higher LoA, respectively.

Correlations were performed between each functional mobility measure and the corresponding MEP measured during it development. None of the correlations explored revealed statistically significant differences, except for the 10-metre Walk Test, even though the correlation coefficient revealed a weak negative association. The results stemming from the correlation analyses are available in Table 3. Other demographical and clinical variables, as Kellgren-Lawrence, BMI, age, or duration of symptoms did not significantly correlate with values of MEP (with *p*-values of 0.251, 0.336, 0.148, 0.362, respectively); age was not associated either (Student's *t*-test, p-value = 0.384), taking the MEP for the 6MWT as the standard for MEP.

A post-hoc power analysis was performed, based on the sample size ($n = 59$) and the effect size of the differences between PAR and MEP during the performance of the 6MWT (Cohen's $d = 1.271$; effect-size $r = 0.536$), with a subsequent power of 0.9.

4 | DISCUSSION

The aims of the current study were (1) to explore and describe the association between self-reported pain at rest and movement-evoked pain and (2) to assess the association between different performance-based tests and their corresponding levels of movement-evoked pain in patients affected by knee osteoarthritis.

To the best of our knowledge, this research represents one of the trailblazing studies in exploring the association between PAR and MEP. The importance of MEP lies in the fact that it assesses pain during activity avoiding any possible recall bias (Previtali et al., 2022) and, furthermore, given that the underlying mechanisms are different to those explaining PAR (Corbett et al., 2019), this specific type of pain could correspond to a different construct than that from PAR: the results stemming from our study support and endorse this hypothesis. When compared to the results by Overton et al. (2023), our results point in a diametrically opposite direction, since Overton states an existing association between both constructs. But two main differences arise in this comparison: first, Overton's study does not focus on PAR, but on different measures of pain (through questionnaires and outcome scores) while we studied the specific association between PAR and MEP. Second, in our study, we used four mobility tests involving walking, to comply with the definition recently expounded by Fullwood et al. (2021) ('pain during walking').

The correlation of the four MEP measures with pain at rest displayed poor results in terms strength of association but, furthermore, no correlation was statistically significant except for the MEP in the TUGT. While the MEP-related measures highly correlated among themselves,

TABLE 2 Correlations: movement-evoked pain versus pain at rest ($n=59$).

	Pain at rest	MEP timed up and go test	MEP 10-metre walk test	MEP 2-minute walk test	MEP 6-minute walk test
Pain at rest		0.237 (0.022)	0.307 (0.018)	0.233 (0.084)	0.257 (0.054)
MEP timed up and go test	0.237 (0.022)		0.577 (0.001)	0.643 (0.001)	0.647 (0.001)
MEP 10-metre walk test	0.307 (0.018)	0.577 (0.001)		0.761 (0.001)	0.760 (0.001)
MEP 2-minute walk test	0.233 (0.084)	0.643 (0.001)	0.761 (0.001)		0.921 (0.001)
MEP 6-minute walk test	0.257 (0.054)	0.647 (0.001)	0.760 (0.001)	0.921 (0.001)	

Note: Each case shows: correlation coefficient (*p*-value).

Abbreviation: MEP, movement-evoked pain.

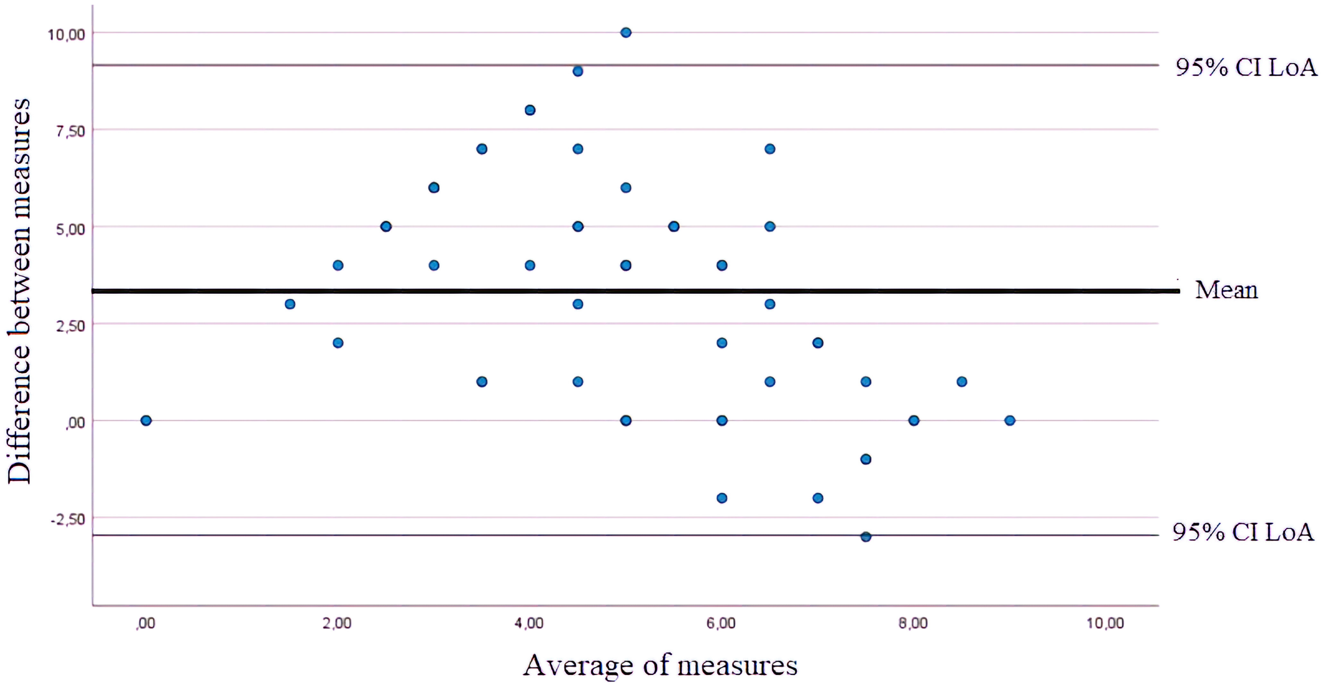

FIGURE 1 Agreement between Pain at Rest and Movement-Evoked Pain. Brief description: Bland–Altman plot to assess agreement between Pain at Rest and Movement-Evoked Pain from the 6-Minute Walk Test. Main findings: The visual inspection of the plot reveals that the difference is not even close to zero, therefore indicating that the two methods are systematically producing different results. The average discrepancy between methods (i.e. the bias) corresponds to more than three points over 10, therefore entailing a bias that corresponds to more than 30% of the measurement range of the variable pain. General conclusion: Our results suggest that both variables are different and do not measure the same construct.

TABLE 3 Correlation between measures of functional mobility performance and their corresponding levels of movement-evoked pain ($n=59$).

Performance vs. MEP	Correlation	Coefficient	*p*-value
Timed up and go test	Kendall	0.061	0.600
10-metre walk test	Spearman	−0.388	0.002
2-minute walk test	Pearson	−0.169	0.212
6-minute walk test	Spearman	−0.241	0.071

Abbreviation: MEP, movement-evoked pain.

the ideas that PAR is not related to MEP and that both PAR and MEP measure different pain-constructs crystallize. The Bland–Altman plot analysed was created with the aim of testing agreement: correlation explores the presence/absence of an association between two different variables, but it does not necessarily depict agreement. The Bland–Altman plot, thus, was built to explore the agreement, (i.e. the level of concordance between two measurements of one variable), to ascertain whether PAR and MEP are indeed measuring the same variable or not. A perfect agreement would correspond to a plot in which the points perfectly lie along the line of equality (Giavarina, 2015; Ranganathan et al., 2017). The visual inspection of the plot reveals that the difference is not even close to zero, therefore indicating that the two methods are systematically producing different results. The average discrepancy between methods (i.e. the bias) corresponds to more than three points over 10, therefore entailing a bias that corresponds to more than 30% of the measurement range of the variable pain: this difference is enormous, from a clinical perspective, when compared to the clinically relevant change explored in other studies for VAS in KOA with results of 0.84 (Eberle & Ottillinger, 1999), or the minimally clinical important difference of 2.26 stated by other authors on the knee (Danoff et al., 2018). The limits of agreement were also very wide (due to the high Standard Deviation), fact that reveals ambiguity in the potential equivalence of both measuring methods. No trend is observed whatsoever, since the difference between methods does not tend to get larger (or smaller) as the average increases. In other words, our results suggest that both variables are different and do not measure the same construct.

Concerning the correlation between each performance test and its linked MEP, no association was found between the performance of the test and the associated MEP, except for the 10-m Walk Test, for which the strength of the correlation was weak. The absence of association between the performance of a mobility test involving walking in a patient and his/her perceived level of pain during the execution and development of the test is therefore stated. This result is not only contrary to the results found by Overton et al. (2023), but it might even seem counterintuitive. In this framework, the explanation of this lack of association could lie on the theories of motor adaptation to pain postulated by Hodges and Tucker (2011) a decade ago, which are based on the basic premise that movement is modified by the nervous system with the purposeful intention of decreasing the nociceptive input and pain, and with the secondary objective of protecting structures from further injuries. In other words, movement tends to 'adapt' during pain, fact that is assumed to reduce the nociceptive input but, furthermore, as recently found, this pain reduction is achieved with 'taking action' to relieve pain and does not specifically depend on reduced noxious stimulus (Bergin et al., 2021). This approach could also explain, for instance, the results from a recent study performed among runners with a history of unilateral knee surgery in which pain during the test (MEP during three trials of the hop for distance and one trial of the side hop test) was not related to functional performance (Mentiplay et al., 2022).

The results stemming from our study should be interpreted in the light of its methodological limitations. First, a high percentage of patients used assistive devices to walk. This situation, although considered and permitted in the different guidelines of the functional tests performed, could have had an impact on the pain experienced by the patient, since it allows the participant to 'adapt' his/her biomechanics to avoid pain and enhance functional performance. Even though, an analysis of the subset of patients with assistive devices displayed results very similar to those from the whole sample, therefore stating that no differences existed, in our study, in terms of the associations shown and expounded, between patients with and/or without devices. Second, MEP in TUGT was categorized in three different strata (under 10 s, 10-to-20 s, over 20 s). The possibility of having the actual time in seconds could have improved the quality of the analyses performed, despite the fact that the results stemming from the analyses of the TUGT are in line with the extant three functional performance tests performed. Third, the sample size of our study was relatively small. We based our initial estimation in the rule of thumb by Fraenkel et al. (2011), who suggest a minimum sample size of 50 subjects for correlational studies. Moreover, once the study conducted and performed, we calculated the post-hoc power analysis, which was roughly of 0.90 (90%), higher than the usual threshold of 0.80. Following the indications provided elsewhere (Hulley et al., 2013) as of the effect size obtained, the minimum sample size needed would be 25 subjects, vastly below our sample size (59 subjects). Therefore, the high effect sizes obtained justify the relevance of the results stemming from a sample of $n = 59$, since the post-hoc power calculation revealed optimal values for the power of the study. Despite the controversial applicability of post-hoc power analysis, we applied a method conceptually sound to gauge variability of statistical findings and thus inform reliability of such findings (Quach et al., 2022). Fourth, the general low level of MEP throughout the tasks may indicate that the 'burden' of this movement-based activities was not enough to elicit MEP in these subjects. Further definition of a set of activities to measure MEP may increase and enhance the measurement of MEP, since this lack of standardization in the measurement threatens trial precision and ability to identify interventions with the most clinically relevant effects on pain: the standardization and operationalization of the concept 'movement-evoked pain' is not fully delimited yet. We followed the initial definition by Graven-Nielsen and Arendt-Nielsen, (2010) and the recent 'update' by Fullwood et al. (2021), but standardizing the measurement of the MEP should also be a cornerstone of the challenging future study of pain, as suggested elsewhere (Srikandarajah & Gilron, 2011). Finally, a high percentage of our sample corresponded to subjects classified as grade II or III according to the Kellgren-Lawrence classification. This fact is nonetheless congruent with other studies with similar characteristics (Alghadir et al., 2015; Previtali et al., 2022) and it is, moreover, in line with the description of the degrees themselves, since degree I is commonly asymptomatic, and the radiographic findings are usually doubtful, while degree IV is usually severe in terms of burden and subjects in this stage are commonly derived to surgical management.

The results of our research reinforce the idea that the two variables analysed measure two different constructs in KOA. Further research shall focus and delve into MEP to better operationalize the term, as well as to develop longitudinal designs to explore the predictive capacity of this emerging measure as a potential proxy of disability, as recently suggested by Simon et al. (2023). Our results reinforce the importance of adopting therapeutic exercise, as a movement-driven therapy, for the management of KOA, since the associated pain is considerably lower than that from pain at rest, alongside providing a positive effect on pain and physical function in subjects affected by KOA (Holden et al., 2023).

Overall, the study and inclusion of MEP in clinical research and measurement should be prioritized, not only to expand the knowledge on the multispectral concept of pain, but also from a biomechanical and gait perspective, since recent studies advocate for the fact that MEP accounts for a significant amount of variance in gait performance in older adults and, as such, it should be considered in the development of future physical function pain assessments and treatments (Murillo et al., 2022). Furthermore, and considering both the fact that movement-evoked pain is directly driven by movement, as well as the importance that exercise therapy is earning cross-sectionally in different conditions, MEP emerges as an outcome measure of paramount importance to be tracked and assessed (Leemans et al., 2022).

5 | CONCLUSION

Movement-evoked pain is neither related to pain at rest nor to functional performance in patients affected by knee osteoarthritis. The results from our study suggest that movement-evoked pain and pain at rest measure and refer to different constructs in knee osteoarthritis. Further studies shall focus on the emerging concept of movement-evoked pain to better operationalize and explore the potential predictive capacity with respect to disability. The implementation of movement-evoked pain as an outcome in exercise-therapy could enhance the tracking of results, as well as the development of tailored interventions under different conditions.

AUTHOR CONTRIBUTIONS

Conceptualization (JLM, MGS, JMH), Data curation (JLM, JMH), Formal Analysis (MGS, JMH), Funding acquisition (JLM), Investigation (JLM, MGS, JMH), Methodology (JLM, MGS, JMH), Project administration (JLM, MGS, JMH). Software (MGS), Validation (JLM, JMH, MGS). All authors critically revised the manuscript for intellectual content and read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to report.

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REFERENCES

Ahmed, H., Kishore, K., Bhat, P., Alghadir, A. H., & Iqbal, A. (2022). Impact of work-related chronic low back pain on functional performance and physical capabilities in women and men: A sex-wise comparative study. *BioMed Research International*, *2022*, 1–9. https://doi.org/10.1155/2022/6307349

Alghadir, A., Anwer, S., & Brismée, J. M. (2015). The reliability and minimal detectable change of Timed Up and Go test in individuals with grade 1–3 knee osteoarthritis. *BMC Musculoskeletal Disorders*, *16*, 174. https://doi.org/10.1186/s12891-015-0637-8

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., Christy, W., Cooke, T. D., Greenwald, R., Hochberg, M., Howell, D., Kaplan, D., Koopman, W., Longley, S., Mankin, H., McShane, D. J., Medsger, T., Meenan, R., Mikkelsen, W., … Wolfe, F. (1986). Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. *Arthritis and Rheumatism*, *29*(8), 1039–1049. https://doi.org/10.1002/art.1780290816

Amatachaya, S., Naewla, S., Srisim, K., Arrayawichanon, P., & Siritaratiwat, W. (2014). Concurrent validity of the 10-meter walk test as compared with the 6-minute walk test in patients with spinal cord injury at various levels of ability. *Spinal Cord*, *52*(4), 333–336. https://doi.org/10.1038/sc.2013.171

ATS Statement. (2002). Guidelines for the six-minute walk test. *American Journal of Respiratory and Critical Care Medicine*, *166*(1), 111–117. https://doi.org/10.1164/ajrccm.166.1.at1102

Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J., & Stitt, L. W. (1988). Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *The Journal of Rheumatology*, *15*(12), 1833–1840.

Bergin, M., Tucker, K., Vicenzino, B., & Hodges, P. W. (2021). "Taking action" to reduce pain—Has interpretation of the motor adaptation to pain been too simplistic? *PLoS One*, *16*(12), e0260715. https://doi.org/10.1371/journal.pone.0260715

Booker, S., Cardoso, J., Cruz-Almeida, Y., Sibille, K. T., Terry, E. L., Powell-Roach, K. L., Riley, J. L., Goodin, B. R., Bartley, E. J., Addison, A. S., Staud, R., Redden, D., Bradley, L., & Fillingim, R. B. (2019). Movement-evoked pain, physical function, and perceived stress: An observational study of ethnic/racial differences in aging non-Hispanic Blacks and non-Hispanic Whites with knee osteoarthritis. *Experimental Gerontology*, *124*, 110622. https://doi.org/10.1016/j.exger.2019.05.011

Cheng, D. K., Nelson, M., Brooks, D., & Salbach, N. M. (2020). Validation of stroke-specific protocols for the 10-meter walk test and 6-minute walk test conducted using 15-meter and 30-meter walkways. *Topics in Stroke Rehabilitation*, *27*(4), 251–261. https://doi.org/10.1080/10749357.2019.1691815

Corbett, D. B., Simon, C. B., Manini, T. M., George, S. Z., Riley, J. L., & Fillingim, R. B. (2019). Movement-evoked pain: Transforming the way we understand and measure pain. *Pain*, *160*(4), 757–761. https://doi.org/10.1097/j.pain.0000000000001431

Cruz-Almeida, Y., Cardoso, J., Riley, J. L., Goodin, B., King, C. D., Petrov, M., Bartley, E. J., Sibille, K. T., Glover, T. L., Herbert, M. S., Bulls, H. W., Addison, A., Staud, R., Redden, D., Bradley, L. A., & Fillingim, R. B. (2017). Physical performance and movement-evoked pain profiles in community-dwelling individuals at risk for knee osteoarthritis. *Experimental Gerontology*, *98*, 186–191. https://doi.org/10.1016/j.exger.2017.08.026

Dailey, D. L., Frey Law, L. A., Vance, C. G. T., Rakel, B. A., Merriwether, E. N., Darghosian, L., Golchha, M., Geasland, K. M., Spitz, R., Crofford, L. J., & Sluka, K. A. (2016). Perceived function and physical performance are associated with pain and fatigue in women with fibromyalgia. *Arthritis Research & Therapy*, *18*(1), 68. https://doi.org/10.1186/s13075-016-0954-9

Danoff, J. R., Goel, R., Sutton, R., Maltenfort, M. G., & Austin, M. S. (2018). How much pain is significant? Defining the minimal clinically important difference for the visual analog scale for pain after total joint arthroplasty. *The Journal of Arthroplasty*, *33*(7), S71–S75.e2. https://doi.org/10.1016/j.arth.2018.02.029

Davis, A. M., King, L. K., Stanaitis, I., & Hawker, G. A. (2022). Fundamentals of osteoarthritis: Outcome evaluation with patient-reported measures and functional tests. *Osteoarthritis and Cartilage*, *30*(6), 775–785. https://doi.org/10.1016/j.joca.2021.07.016

Eberle, E., & Ottillinger, B. (1999). Clinically relevant change and clinically relevant difference in knee osteoarthritis. *Osteoarthritis and Cartilage*, *7*(5), 502–503. https://doi.org/10.1053/joca.1999.0246

Fraenkel, J. R., Wallen, N. E., & Hyun, H. H. (2011). *How to design and evaluate research in education* (8th ed.). Mc Graw Hill. ISBN: 978-0-07-809785-0.

Fullwood, D., Means, S., Merriwether, E. N., Chimenti, R. L., Ahluwalia, S., & Booker, S. Q. (2021). Toward understanding movement-evoked pain (MEP) and its measurement: A scoping review. *The Clinical Journal of Pain*, *37*(1), 61–78. https://doi.org/10.1097/AJP.0000000000000891

Gacto-Sánchez, M., Lozano-Meca, J. A., Lozano-Guadalajara, J. V., & Montilla-Herrador, J. (2023). Concurrent validity of the 2-and 6-minute walk test in knee osteoarthritis. *The Knee*, *43*, 34–41. https://doi.org/10.1016/j.knee.2023.05.009

GBD 2021 Osteoarthritis Collaborators. (2023). Global, regional, and national burden of osteoarthritis, 1990–2020 and projections to 2050: A systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatology*, *5*(9), e508–e522. https://doi.org/10.1016/S2665-9913(23)00163-7

Giavarina, D. (2015). Understanding Bland Altman analysis. *Biochemia Medica*, *25*(2), 141–151. https://doi.org/10.11613/BM.2015.015

Gijbels, D., Eijnde, B., & Feys, P. (2011). Comparison of the 2- and 6-minute walk test in multiple sclerosis. *Multiple Sclerosis Journal*, *17*(10), 1269–1272. https://doi.org/10.1177/1352458511408475

Goldman, M. D., Marrie, R. A., & Cohen, J. A. (2008). Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Multiple Sclerosis Journal*, *14*(3), 383–390. https://doi.org/10.1177/1352458507082607

Graven-Nielsen, T., & Arendt-Nielsen, L. (2010). Assessment of mechanisms in localized and widespread musculoskeletal pain. *Nature Reviews Rheumatology*, *6*(10), 599–606. https://doi.org/10.1038/nrrheum.2010.107

Hodges, P. W., & Tucker, K. (2011). Moving differently in pain: A new theory to explain the adaptation to pain. *Pain*, *152*(3), S90–S98. https://doi.org/10.1016/j.pain.2010.10.020

Holden, M. A., Hattle, M., Runhaar, J., Riley, R. D., Healey, E. L., Quicke, J., van der Windt, D. A., Dziedzic, K., van Middelkoop, M., Burke, D., Corp, N., Legha, A., Bierma-Zeinstra, S., Foster, N. E., Brown, J., Ingram, C., Hickson, S., Taylor, R., Walker, C., … Yilmaz Menek, M. (2023). Moderators of the effect of therapeutic exercise for knee and hip osteoarthritis: A systematic review and individual participant data meta-analysis. *The Lancet Rheumatology*, *5*(7), e386–e400. https://doi.org/10.1016/s2665-9913(23)00122-4

Hulley, S. B., Cummings, S. R., Browner, W. S., Grady, D., & Newman, T. B. (2013). *Designing clinical research: An epidemiologic approach* (4th ed., p. 79). Lippincott Williams & Wilkins. Appendix 6C.

Hunter, D. J., & Bierma-Zeinstra, S. (2019). Osteoarthritis. *The Lancet*, *393*(10182), 1745–1759. https://doi.org/10.1016/S0140-6736(19)30417-9

Hutchison, L., Grayson, J., Hiller, C., D'Souza, N., Kobayashi, S., & Simic, M. (2023). Relationship between knee biomechanics and pain in people with knee osteoarthritis: A systematic review and meta-analysis. *Arthritis Care & Research*, *75*(6), 1351–1361. https://doi.org/10.1002/acr.25001

Lee, S.-H., Kao, C.-C., Liang, H.-W., & Wu, H.-T. (2022). Validity of the Osteoarthritis Research Society International (OARSI) recommended performance-based tests of physical function in individuals with symptomatic Kellgren and Lawrence grade 0–2 knee osteoarthritis. *BMC Musculoskeletal Disorders*, *23*(1), 1040. https://doi.org/10.1186/s12891-022-06012-2

Leemans, L., Polli, A., Nijs, J., Wideman, T., Den Bandt, H., & Beckwée, D. (2022). It hurts to move! Intervention effects and assessment methods for movement-evoked pain in patients with musculoskeletal pain: A systematic review with meta-analysis. *Journal of Orthopaedic & Sports Physical Therapy*, *52*(6), 345–374. https://doi.org/10.2519/jospt.2022.10527

Lespasio, M. J., Piuzzi, N. S., Husni, M. E., Muschler, G. F., Guarino, A., & Mont, M. A. (2017). Knee osteoarthritis: A primer. *The Permanente Journal*, *21*(4), 16–183. https://doi.org/10.7812/TPP/16-183

Litcher-Kelly, L., Martino, S. A., Broderick, J. E., & Stone, A. A. (2007). A systematic review of measures used to assess chronic musculoskeletal pain in clinical and randomized controlled clinical trials. *The Journal of Pain*, *8*(12), 906–913. https://doi.org/10.1016/j.jpain.2007.06.009

McBeth, J., Nicholl, B. I., Cordingley, L., Davies, K. A., & Macfarlane, G. J. (2010). Chronic widespread pain predicts physical inactivity: Results from the prospective EPIFUND study. *European Journal of Pain*, *14*(9), 972–979. https://doi.org/10.1016/j.ejpain.2010.03.005

Mentiplay, B., Girdwood, M., Johnston, R., de Oliveira Silva, D., Culvenor, A., Hedger, M., West, T., Telles, G., Haberfield, M., & Crossley, K. (2022). Functional performance in runners after knee surgery: Differences between limbs and relationships with pain and confidence. *Journal of Science and Medicine in Sport*, *25*, S64–S65. https://doi.org/10.1016/j.jsams.2022.09.076

Mishra, P., Pandey, C., Singh, U., Gupta, A., Sahu, C., & Keshri, A. (2019). Descriptive statistics and normality tests for statistical data. *Annals of Cardiac Anaesthesia*, *22*(1), 67–72. https://doi.org/10.4103/aca.ACA_157_18

Murillo, B. C., Lipat, A. L., Peterson, J. A., & Cruz-Almeida, Y. (2022). The influence of movement-evoked pain on lower extremity physical function in older adults. *The Journal of Pain*, *23*(5), 47. https://doi.org/10.1016/j.jpain.2022.03.179

Overton, M., Swain, N., Falling, C., Gwynne-Jones, D., Fillingim, R., & Mani, R. (2023). Activity-related pain predicts pain and functional outcomes in people with knee osteoarthritis: A longitudinal study. *Frontiers in Pain Research*, *3*, 1082252. https://doi.org/10.3389/fpain.2022.1082252

Previtali, D., Andriolo, L., Di Laura Frattura, G., Boffa, A., Candrian, C., Zaffagnini, S., & Filardo, G. (2020). Pain trajectories in knee osteoarthritis—A systematic review and best evidence synthesis on pain predictors. *Journal of Clinical Medicine*, *9*(9), 2828. https://doi.org/10.3390/jcm9092828

Previtali, D., Boffa, A., Di Martino, A., Deabate, L., Delcogliano, M., & Filardo, G. (2022). Recall bias affects pain assessment in knee osteoarthritis: A pilot study. *Cartilage*, *13*(4), 50–58. https://doi.org/10.1177/19476035221118417

Quach, N. E., Yang, K., Chen, R., Tu, J., Xu, M., Tu, X. M., & Zhang, X. (2022). Post-hoc power analysis: A conceptually valid approach for power based on observed study data. *General Psychiatry*, *35*, e100764. https://doi.org/10.1136/gpsych-2022-100764

Ranganathan, P., Pramesh, C., & Aggarwal, R. (2017). Common pitfalls in statistical analysis: Measures of agreement. *Perspectives in Clinical Research*, *8*(4), 187. https://doi.org/10.4103/picr.PICR_123_17

Ro, D. H., Lee, J., Lee, J., Park, J.-Y., Han, H.-S., & Lee, M. C. (2019). Effects of knee osteoarthritis on hip and ankle gait mechanics. *Advances in Orthopedics*, *2019*, 1–6. https://doi.org/10.1155/2019/9757369

Sayers, A., Wylde, V., Lenguerrand, E., Beswick, A. D., Gooberman-Hill, R., Pyke, M., Dieppe, P., & Blom, A. W. (2016). Rest pain and movement-evoked pain as unique constructs in hip and knee replacements. *Arthritis Care & Research*, *68*(2), 237–245. https://doi.org/10.1002/acr.22656

Schober, P., Boer, C., & Schwarte, L. A. (2018). Correlation coefficients: Appropriate use and interpretation. *Anesthesia & Analgesia*, *126*(5), 1763–1768. https://doi.org/10.1213/ANE.0000000000002864

Serpas, D. G., Zettel-Watson, L., & Cherry, B. J. (2022). Pain intensity and physical performance among individuals with fibromyalgia in mid-to-late life: The influence of depressive symptoms. *Journal of Health Psychology*, *27*(7), 1723–1737. https://doi.org/10.1177/13591053211009286

Simon, C. B., Hicks, G. E., Pieper, C. F., Byers Kraus, V., Keefe, F. J., & Colón-Emeric, C. (2023). A novel movement-evoked pain provocation test for older adults with persistent low Back pain: Safety, feasibility, and associations with self-reported physical function and usual gait speed. *The Clinical Journal of Pain*, *39*(4), 166–174. https://doi.org/10.1097/AJP.0000000000001101

Srikandarajah, S., & Gilron, I. (2011). Systematic review of movement-evoked pain versus pain at rest in postsurgical clinical trials and meta-analyses: A fundamental distinction requiring standardized measurement. *Pain*, *152*(8), 1734–1739. https://doi.org/10.1016/j.pain.2011.02.008

Yázigi, F., Espanha, M., Marques, A., Teles, J., & Teixeira, P. (2018). Predictors of walking capacity in obese adults with knee osteoarthritis. *Acta Reumatológica Portuguesa*, *43*(4), 256–263.

Zhang, W., Doherty, M., Peat, G., Bierma-Zeinstra, M. A., Arden, N. K., Bresnihan, B., Herrero-Beaumont, G., Kirschner, S., Leeb, B. F., Lohmander, L. S., Mazières, B., Pavelka, K., Punzi, L., So, A. K., Tuncer, T., Watt, I., & Bijlsma, J. W. (2010). EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Annals of the Rheumatic Diseases*, *69*(3), 483–489. https://doi.org/10.1136/ard.2009.113100

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