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Neuropathic pain associated with first metatarsophalangeal joint osteoarthritis: frequency and associated factors

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/acr.25125

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Funding: This study was funded by a project grant from the National Health and Medical Research Council of Australia (ID: 1105244).

Declaration of interests: None of the authors has a competing interest to declare.

ABSTRACT

Objective: To determine whether neuropathic pain is a feature of first metatarsophalangeal (MTP) joint osteoarthritis (OA).

Methods: Ninety-eight participants (mean age 57.4 years, standard deviation 10.3) with symptomatic radiographic first MTP joint OA completed the painDETECT questionnaire (PDQ), which incorporates nine questions regarding the intensity and quality of pain. The likelihood of neuropathic pain was determined using established cut-points of the PDQ. Participants with unlikely neuropathic pain were then compared to those with possible/likely neuropathic pain in relation to age, sex, general health (Short Form [SF] 12), psychological wellbeing (Depression, Anxiety and Stress Scale), pain characteristics (self-efficacy, duration, and severity), foot health (Foot Health Status Questionnaire [FHSQ]), first MTP dorsiflexion range of motion and radiographic severity. Effect sizes (Cohen's *d*) were also calculated.

Results: Thirty (31%) participants had possible/likely neuropathic pain (possible n=19, [19.4%], likely n=11 [11.2%]). The most common neuropathic symptoms were sensitivity to pressure (56%), sudden pain attacks/electric shocks (36%) and burning (25%). Compared to those with unlikely neuropathic pain, those with possible/likely neuropathic pain were significantly older (d=0.59, p=0.010), had worse SF12 physical (d=1.10, p<0.001), pain self-efficacy (d=0.98, p<0.001), FHSQ pain (d=0.98, p<0.001) and FHSQ function (d=0.82, p<0.001) scores, and had higher pain severity at rest (d=1.01, p<0.001).

Conclusion: A significant proportion of individuals with first MTP joint OA report symptoms suggestive of neuropathic pain, which may partly explain the suboptimal responses to commonly used treatments for this condition. Screening for neuropathic pain may assist in the selection of targeted interventions and improve clinical outcomes.

Key words: osteoarthritis; foot; neuropathic pain

Significance and Innovations

- This is the first study to evaluate neuropathic pain in people with foot osteoarthritis (OA)
- One in three people with first metatarsophalangeal joint OA had evidence of possible or likely neuropathic pain
- Those with neuropathic pain were older, had worse general physical health, worse foot health, and greater pain severity at rest
- Screening for neuropathic pain may assist in the selection of appropriate interventions

Pain is the most common and disabling symptom of osteoarthritis (OA) and has primarily been attributed to local tissue damage leading to mechanical and/or inflammatory stimulation of peripheral sensory neurons (nociceptors) in joint tissues (1). However, the suboptimal and variable response to treatment of OA-related pain has led to a reappraisal of its underlying causes, and the contribution of non-nociceptive pathways is being increasingly recognised (2, 3). In particular, neuropathic pain, defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (4), may be responsible for symptoms such as tingling, numbness, burning and electrical shock sensations (5), which are experienced by approximately one-third of people with knee or hip OA (6).

The presence of neuropathic symptoms increases the individual burden of knee OA, as it is associated with more severe pain (7-10), greater impairment in physical function (9-13), worse quality of life (10, 11, 13, 14) and poorer sleep quality (10). Several person-level factors have been shown to be associated with neuropathic pain in people with knee OA, including increased age (13), higher body mass index (13), female sex (8), multiple comorbidities (8), pain at multiple sites (7, 12), referred pain (7) and hyperalgesia (9). Knee joint-specific correlates of neuropathic pain include meniscal lesions (15) and prior surgery (10), although reported associations with radiographic severity are inconsistent (12, 13, 16).

To the best of our knowledge, no studies have examined neuropathic pain related to OA affecting the joints of the foot. This is an important omission, as foot OA has a similar prevalence to knee OA (17), is considered disabling in three-quarters of patients (17), and is a common reason for consultation in primary care (18). Foot OA most commonly affects the first metatarsophalangeal (MTP) joint and is characterised by the formation of a dorsal exostosis (19), limited range of motion (20) and altered walking patterns (21). Interventions such as footwear and orthoses have been shown to alter the biomechanical function of the foot in individuals with first MTP joint OA (22, 23), but have demonstrated only modest reductions in pain (24, 25), suggesting that non-mechanical factors may contribute to symptoms.

Therefore, the objectives of this study were to determine whether neuropathic pain is a feature of first MTP joint OA, and to explore person- and foot-level factors associated with the presence of neuropathic pain in participants enrolled in a recent randomized clinical trial.

METHODS

Participants

Participants for this study were drawn from a randomized trial that evaluated the effectiveness of shoe-stiffening inserts for first MTP joint OA. Full details of the trial have been published (25, 26). Participants were recruited via advertisements in local newspapers, posters placed in senior citizens' centres and retirement villages, mail-out advertisements to health-care practitioners, mail-out to people currently accessing podiatry services at the La Trobe University Health Sciences Clinic, and through social media. To be included in the trial, participants needed to be aged 18 years of age or older, have pain in the first MTP joint on most days for at least 12 weeks, rated at least 30 mm on a 100 mm visual analogue scale, have pain upon palpation of the dorsal aspect of the first MTP joint, have restricted first MTP joint dorsiflexion, and be able to walk household distances without the use of a walking aid. Participants were excluded if they had previous first MTP joint surgery, were currently pregnant, or had hallux valgus, a systemic inflammatory condition or cognitive impairment. Ethical approval was provided by the La Trobe University Human Ethics Committee (HEC15-128) and written informed consent was obtained from all participants. The sample size for this study was dictated by the requirements of the randomized trial, which was powered to detect a minimum clinically important difference in the primary outcome measure, the Foot Health Status Questionnaire pain subscale (25, 26).

Demographic, General Health and Pain Assessments

A structured questionnaire was used to collect data on participant demographics (age and sex), general health (the Short Form 12 questionnaire (27)), psychological well-being (the Depression, Anxiety and Stress Scale (28)), pain characteristics (including the Pain Self-Efficacy Questionnaire (29), pain duration and pain severity at rest and while walking (26)), and foot health (the Foot Health Status Questionnaire pain and function subscales (30)). Only baseline data were used in this analysis.

Clinical and Radiographic Assessments

Height and weight were measured using a stadiometer and digital scales and body mass index was calculated as weight (kg)/height $(m)^2$. Clinical features associated with first MTP joint OA (pain on palpation, dorsal exostosis, joint effusion, pain on motion, hard-end feel and crepitus)

and passive, non-weightbearing first MTP joint dorsiflexion range of motion were documented using established techniques (19). The presence of radiographic first MTP joint OA was determined using the La Trobe University radiographic atlas, which incorporates weightbearing dorso-plantar and lateral radiographs to document the presence of OA based on observations of osteophytes and joint space narrowing (31). Radiographic OA was documented as present or absent based on the case definition of the La Trobe University atlas (at least 1 score of 2 for osteophytes or joint space narrowing from either the dorsoplantar or lateral view) (32), and radiographic OA severity was documented as mild (no scores for osteophytes or joint space narrowing from either view >1), moderate (at least one score of 2 but none >2), or severe (at least one score of 3) (20).

Neuropathic Pain Assessment

To document the presence of neuropathic pain affecting the first MTP joint, we used the self-reported painDETECT Questionnaire (PDQ), which was originally developed to discriminate between nociceptive and neuropathic pain in people with chronic low back pain (33). The PDQ comprises seven items evaluating pain quality (scored 0 to 5), one item evaluating pain pattern (scored -1 to 1), and one item evaluating pain radiation (scored 0 to 2). Individual question scores are summed to calculate a total score ranging from -1 to 38. Total scores <13 indicate that neuropathic pain is unlikely, scores from 13 to 18 indicate that neuropathic pain is possible, and scores >18 indicate that neuropathic pain is likely (34). The PDQ has been validated against expert physician diagnosis of neuropathic pain in people with low back pain (33) and against quantitative sensory testing for the detection of central sensitization in people with knee OA (35).

Statistical Analysis

Statistical analysis was undertaken using IBM SPSS Statistics version 26.0 (IBM Corp, NY, USA). All data were explored for normality, and none required transformation. For continuously scored variables, differences between participants with and without neuropathic pain were compared using independent samples *t*-tests and effect sizes (Cohen's *d*). The following interpretation of effect sizes was used: ≤0.01 = very small, >0.01 to 0.20 = small, >0.20 to 0.50 = medium, >0.50 to 0.8 = large, >0.80 to 1.2 = very large, and >1.20 = huge (36).

For dichotomous or ordinal variables, differences between groups were calculated using the chi-squared statistic.

RESULTS

Participants

One hundred participants were recruited for the randomized trial (25). Of these, 98 had complete PDQ data and were included in this analysis (44 men and 54 women, mean age 57.3 [SD 10.3] years). Characteristics of these participants are reported in Table 1. Data were missing for the following variables: height, weight, and body mass index (n=3), dorsoplantar radiographs (n=5) and lateral radiographs (n=6).

Neuropathic Pain Characteristics

Responses to the PDQ are shown in Table 2. Sixty-nine participants (70%) reported at least one neuropathic symptom with at least moderate severity, with the most common neuropathic symptoms being sensitivity to pressure (n=55; 56%), sudden pain attacks/electric shocks (n=35; 36%) and burning (n=24; 25%). Thirty-seven participants (37.8%) reported pain radiation. Thirty (31%) participants had possible/likely neuropathic pain (possible n=19, [19.4%], likely n=11 [11.2%]), as defined by the overall PDQ score.

Differences between Participants With and Without Neuropathic Pain

Participant characteristics in those with and without neuropathic pain are shown in Table 3. Compared to those with unlikely neuropathic pain, those with possible/likely neuropathic pain were significantly older (d=0.59, p=0.010; large effect size [ES]), had worse scores on the SF12 physical (d=1.10, p<0.001; very large ES), PSEQ (d=0.98, p<0.001; very large ES), FHSQ pain (d=0.98, p<0.001; very large ES) and FHSQ function (d=0.82, p<0.001; very large ES) questionnaires, and had higher pain severity at rest (d=1.01, p<0.001; very large ES).

DISCUSSION

This study sought to determine whether neuropathic pain is a feature of foot OA by applying the PDQ to participants with OA affecting the first MTP joint who were enrolled in a randomized trial. We found that 70% of participants reported at least one moderate symptom indicative of neuropathic pain (such as electric shocks, burning, numbness and tingling), and

that the prevalence of possible/likely neuropathic pain in this group using the established overall PDQ cut-off score was 31%. Those with possible/likely neuropathic pain were older, had worse general physical health, worse foot health, and greater pain severity at rest. To the best of our knowledge, this study provides the first insights into neuropathic pain related to foot OA.

The prevalence of neuropathic pain observed in this study is similar to previous reports in people with knee and hip OA. A systematic review and meta-analysis of 39 studies (36 involving the knee and 3 involving the hip) reported a pooled prevalence estimate of 40% (95% confidence interval [CI] 32 to 48) in knee OA and 29% (95% CI 22 to 37) in hip OA, using the same case definition of possible/likely neuropathic pain using the PDQ (6). The prevalence of reporting individual neuropathic symptoms was also high in our study, with 70% reporting at least one neuropathic symptom with at least moderate severity. The most frequently reported symptoms – sensitivity to pressure and sudden electric shocks – are hallmark features of neuropathic pain and are thought to result from central sensitization and spontaneous firing of peripheral nociceptors, respectively (37).

We observed several person-level but few foot-level differences between participants with and without neuropathic pain. Those with neuropathic pain had worse general health (as evidenced by lower SF12 scores) and greater pain severity, which is consistent with previous reports relating to neuropathic pain in people with knee OA using a range of health-related quality of life measures (11, 13, 14) and pain assessment tools (7, 8, 10, 15). Interestingly, we found that although pain severity at rest was higher in those with neuropathic pain, pain during walking was not. This provides further evidence of a centrally-mediated pain process in some participants, as pain severity when walking is typically greater than at rest in first MTP joint OA (25), possibly due to the loads associated with walking leading to mechanical stimulation of sensory neurons in local joint tissues.

The contribution of local, joint-level factors to neuropathic pain in OA is unclear. Although neuropathic pain in people with knee OA is more common in those with meniscal lesions (15) or who have undergone surgery (10), research findings related to the association with radiographic severity are inconsistent (12, 13, 16) and may be confounded by the influence of disease duration. We found no difference between the non-neuropathic and neuropathic groups

in relation to measures of disease severity, including clinical features (such as range of motion, crepitus, or presence of a dorsal exostosis) or the presence and severity of radiographic OA. This is a notable finding, as previous work has demonstrated several dose-response relationships between radiographic severity of first MTP joint OA, range of motion and symptoms, consistent with a longitudinal pattern of progression (20). Taken together, these findings suggest that while local, structural factors may play a role in first MTP joint OA disease progression and symptomatology more broadly, neuropathic symptoms may be more closely related to systematic factors. However, it is also possible that the initial catalyst for OA symptoms is mechanical, and prolonged nociceptive input subsequently leads to neuropathic pain symptoms via central sensitization (5). Indeed, although not reaching statistical significance (p=0.055), participants in our study with possible/likely neuropathic pain had a longer duration of symptoms (mean of 60 months *vs* 39 months).

The key clinical implication of these findings is that there may be some value in screening for neuropathic symptoms in people with first MTP joint OA, as this may influence treatment decisions. Emerging evidence suggests that individuals with neuropathic pain associated with knee OA may be less responsive to commonly used treatments such as physical therapy (38) or joint replacement surgery (39). Although no studies have explored this in relation to foot OA, the presence of neuropathic pain may at least partly explain why only modest improvements in symptoms have been observed in clinical trials of footwear and foot orthoses, interventions that address mechanical deficits associated with first MTP joint OA (24, 25, 40). In those with predominantly neuropathic symptoms, centrally-acting pharmacological treatment approaches may be indicated (2), although only duloxetine, a serotonin-norepinephrine reuptake inhibitor, has sufficient evidence to support its use in OA (41).

Strengths of this study include the well characterised sample with validated clinical and radiographic measures of first MTP joint OA, and a broad array of general health measures. However, our findings need to be considered in the context of several inherent limitations in the study design. First, our participants were drawn from a randomized trial rather than a population-based cohort, so the sample size was relatively small and may not be reflective of the broader population with first MTP joint OA. Second, our case definition of neuropathic pain was based on the PDQ. Although this is a commonly used tool with some evidence of validity, there is currently no gold standard to definitively identify neuropathic pain associated

with OA. We also used the original PDQ rather than the modified version, the latter of which may have better validity as it requests participants to focus on neuropathic symptoms "in or around" their affected joint rather than their "main area of pain", and the pain radiation question was reworded to improve clarity (35). We consider misclassification of neuropathic pain location in our study to be unlikely, as all symptom-related questions in the baseline survey specifically referred to the "big toe joint". However, it is possible that some participants misunderstood the pain radiation question, as some non-adjacent radiation patterns were reported. Third, we did not perform any quantitative sensory testing, which would have provided greater insights into the contribution of central sensitization (42).

In conclusion, in this analysis of data from a clinical trial of people with first MTP joint OA, one in three reported symptoms suggestive of neuropathic pain. Those with possible or likely neuropathic pain were older, had worse general physical health, worse foot health, and greater pain severity at rest. Screening for neuropathic pain may assist in the optimum selection of interventions in clinical practice and may be worthy of consideration when designing clinical trials.

COMPETING INTERESTS

None of the authors has a competing interest to declare.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication.

Study conception and design: Menz, Munteanu, Landorf, Cicuttini, Roddy.

Acquisition of data: Allan, Buldt.

Analysis and interpretation of data: Menz, Munteanu, Landorf, Allan, Buldt, Cicuttini, Roddy.

ACKNOWLEDGEMENTS

HBM is currently a National Health and Medical Research Council Senior Research Fellow (ID: 1135995).

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Table 1. Participant characteristics.*

Demographics and anthropometrics	
Age, mean ± SD years	57.3 ± 10.3
Female	54 (55.1)
Height, mean ± SD cm	168.3 ± 8.2
Weight, mean ± SD kg	79.4 ± 13.0
Body mass index, mean ± SD kg/m^2	28.1 ± 4.6
Clinical features	
Passive NWB first MTP joint maximum dorsiflexion, mean ± SD degrees	45.3 ± 11.2
Pain on palpation	98 (100)
Palpable dorsal exostosis	97 (99.0)
Pain on motion of first MTP joint	74 (75.5)
Hard-end feel when dorsiflexed	92 (93.9)
Crepitus	21 (21.4)
Radiographic first MTP joint OA†	84 (90.3)
Radiographic severity‡	
Mild	9 (9.7)
Moderate	38 (40.9)
Severe	46 (49.5)

* Values are the number (%) unless indicated otherwise. MTP = metatarsophalangeal; NWB = non-weightbearing; OA = osteoarthritis.

† At least 1 score of 2 for osteophytes or joint space narrowing from either view using case definition from La Trobe Radiographic Atlas (31).

‡ Mild: no scores > 1; moderate: at least one score of 2 but none > 2; severe: at least one score of 3 for osteophytes or joint space narrowing from either view, using La Trobe Radiographic Atlas (31).

Table 2. PainDETECT responses.*

Pain severity, mean ± SD (score range 0 to 10)	
How would you assess your pain now, at this moment?	3.76 ± 2.34
How strong was the strongest pain during the past 4 weeks?	7.03 ± 2.02
How strong was the pain during the past 4 weeks on average?	4.96 ± 1.86
Pain pattern	
Persistent pain with slight variations	32 (32.7)
Persistent pain with pain attacks	33 (33.7)
Pain attacks without pain between them	25 (25.5)
Pain attacks with pain between them	8 (8.2)
Pain radiation	37 (37.8)
Pain quality, moderately or more (score ≥ 3/5)	
Burning	24 (24.5)
Tingling or prickling	14 (14.3)
Sensitivity to light touch	18 (18.4)
Sudden pain attacks/electric shocks	35 (35.7)
Sensitivity to cold or heat	10 (10.2)
Numbness	12 (12.2)
Sensitivity to pressure	55 (56.1)
Total painDETECT score, mean ± SD (score range 0 to 38)†	10.7 ± 5.5
Neuropathic pain unlikely	68 (69.4)
Neuropathic pain possible	19 (19.4)
Neuropathic pain likely	11 (11.2)

* Values are the number (%) unless indicated otherwise.

† Total scores <13 indicate that neuropathic pain is unlikely, scores from 13 to 18 indicate that neuropathic pain is possible, and scores >18 indicate that neuropathic pain is likely (34).

Table 3. Participant characteristics in those with and without neuropathic pain affecting the first MTP joint.*

	Non-neuropathic (n=68)	Neuropathic (n=30)	*d*	*p*
Demographics and anthropometrics				
Age, mean ± SD years	55.5 ± 11.0	61.3 ± 7.1	0.59	0.003
Female	34 (50.0)	20 (66.7)	-	0.186
Body mass index, mean ± SD kg/m^2	27.6 ± 4.6	29.3 ± 4.5	0.38	0.092
General health				
SF12 – physical	49.2 ± 8.0	39.9 ± 9.7	1.10	<0.001
SF12 – mental	53.7 ± 9.4	52.5 ± 8.7	0.13	0.543
Psychological wellbeing				
DASS21 – depression	2.9 ± 5.9	4.9 ± 5.7	0.35	0.118
DASS21 – anxiety	3.2 ± 5.3	3.6 ± 4.9	0.08	0.723
DASS21 – stress	7.3 ± 7.4	9.3 ± 8.8	0.26	0.287
Pain characteristics				
PSEQ	54.1 ± 6.0	47.0 ± 9.7	0.98	0.001
Pain duration, months	39 ± 47	60 ± 92	0.35	0.055
Pain severity at rest, VAS	2.4 ± 1.6	4.1 ± 1.9	1.01	<0.001
Pain severity while walking, VAS	5.0 ± 1.5	5.5 ± 1.6	0.33	0.164
Foot health				
FHSQ – pain	51.9 ± 16.1	37.0 ± 13.4	0.98	<0.001
FHSQ – function	71.7 ± 21.6	53.8 ± 23.1	0.82	<0.001
Clinical features				
Passive NWB first MTP joint maximum dorsiflexion, mean ± SD degrees	46.6 ± 10.1	42.2 ± 13.1	0.40	0.108
Pain on palpation	68 (100)	30 (100)	-	NC
Palpable dorsal exostosis	67 (98.5)	30 (100)	-	0.504
Pain on motion of first MTP joint	48 (70.6)	26 (86.7)	-	0.088
Hard-end feel when dorsiflexed	64 (94.1)	28 (93.3)	-	0.881
Crepitus	14 (20.6)	7 (23.3)	-	0.760
Radiographic first MTP joint OA†	59 (90.8)	25 (89.3)	-	0.546
Radiographic severity‡				
Mild	6 (9.2)	3 (10.7)	-	0.965
Moderate	27 (41.5)	11 (39.3)		
Severe	32 (49.2)	14 (50.0)		

* Values are the number (%) unless indicated otherwise.

SF12 = Short Form 12, score range 0 – 100, higher scores indicate better function; DASS21 = 21 item Depression, Anxiety and Stress Scale, score range 0 – 42, higher scores indicate worse function; PSEQ = Pain Self-Efficacy Questionnaire, score range 0 – 60, higher scores indicate greater confidence dealing with pain; VAS = visual analog scale, score range 0 – 10, higher scores indicate worse pain; FHSQ = Foot Health Status Questionnaire, score range 0 – 100, higher scores indicate better function; MTP = metatarsophalangeal; NWB = non-weightbearing; NC = not calculable; OA = osteoarthritis

† At least 1 score of 2 for osteophytes or joint space narrowing from either view using case definition from La Trobe Radiographic Atlas (31).

‡ Mild: no scores > 1; moderate: at least one score of 2 but none > 2; severe: at least one score of 3 for osteophytes or joint space narrowing from either view, using La Trobe Radiographic Atlas (31).