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ORIGINAL RESEARCH

Neuropathic pain in the IMI-APPROACH knee osteoarthritis cohort: prevalence and phenotyping

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ABSTRACT

Objectives Osteoarthritis (OA) patients with a neuropathic pain (NP) component may represent a specific phenotype. This study compares joint damage, pain and functional disability between knee OA patients with a likely NP component, and those without a likely NP component.

Methods Baseline data from the Innovative Medicines Initiative Applied Public-Private Research enabling OsteoArthritis Clinical Headway knee OA cohort study were used. Patients with a painDETECT score ≥19 (with likely NP component, n=24) were matched on a 1:2 ratio to patients with a painDETECT score ≤12 (without likely NP component), and similar knee and general pain (Knee Injury and Osteoarthritis Outcome Score pain and Short Form 36 pain). Pain, physical function and radiographic joint damage of multiple joints were determined and compared between OA patients with and without a likely NP component.

Results OA patients with painDETECT scores ≥19 had statistically significant less radiographic joint damage (p≤0.04 for Knee Images Digital Analysis parameters and Kellgren and Lawrence grade), but an impaired physical function (p<0.003 for all tests) compared with patients with a painDETECT score ≤12. In addition, more severe pain was found in joints other than the index knee (p≤0.001 for hips and hands), while joint damage throughout the body was not different.

Conclusions OA patients with a likely NP component, as determined with the painDETECT questionnaire, may represent a specific OA phenotype, where local and overall joint damage is not the main cause of pain and disability. Patients with this NP component will likely not benefit from general pain medication and/or disease-modifying OA drug (DMOAD) therapy. Reserved inclusion of these patients in DMOAD trials is advised in the quest for successful OA treatments.

Trial registration number
The study is registered under clinicaltrials.gov nr: NCT03883568.

Key messages

What is already known about this subject?

- ► Osteoarthritis (OA) is a heterogeneous disease with multiple causes for similar clinical symptoms.

What does this study add?

- ► In knee OA patients with a likely neuropathic pain component, local joint damage is not the leading cause for pain and disability.

How might this impact on clinical practice or further developments?

- ► Patients with a likely neuropathic pain component reflect a specific OA phenotype, most likely not responding to general analgesics or disease-modifying OA drug (DMOAD) therapy.
- ► These patients need to be identified and offered a more personalised treatment.
- ► Moreover, reserved inclusion of these patients in DMOAD trials is advised.

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INTRODUCTION

Osteoarthritis (OA) is a degenerative joint disease leading to pain, stiffness and loss of function. Despite the increasing prevalence and great burden, there is still no cure. Treatment is focused on relieving symptoms and controlling inflammation if present. Multiple international guidelines recommend the use of topical/oral non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of OA pain, if non-pharmacological interventions fail.[1–3] However, in a meta-analysis evaluating the analgesic efficacy of NSAIDs and selective cyclo-oxygenase-2 inhibitors in knee OA, an effect size of 0.32 was found,[4] suggesting the effect is limited and/or that at least part of the OA patients does not benefit from this approach sufficiently.

A possible explanation for the limited efficacy of current analgesic drugs is the variety in pathophysiologic mechanisms between different OA patients. OA is considered a heterogeneous disease, existing of multiple phenotypes, with different causes for similar clinical symptoms including pain.[5] Pain is currently categorised into nociceptive pain resulting from tissue damage; neuropathic pain (NP), involving nerve damage; and nociplastic pain, which is caused by altered nociception without clear evidence of actual tissue damage.[6] OA pain is classically considered a nociceptive pain that arises from joint tissue damage and inflammation. However, an evident relation between the (radiographic) tissue damage with (reported) pain has not been identified.[7] Not all patients respond to general pain medication, such as acetaminophen, NSAIDs, cyclo-oxygenase-2 inhibitors and tramadol.[8–11] Moreover, in a substantial proportion of knee OA patients, pain persists after removing the damaged tissue during total knee arthroplasty (TKA).[12] These observations indicate that the classification of OA pain as purely nociceptive is erroneous.

Patients with OA who experience pain that is not a pure nociceptive pain but also has neuropathic features could be recognised as a distinct subgroup. Identification of this subgroup, may allow clinicians to improve the management of symptoms of this specific OA phenotype, using distinct treatments focused on this NP component.[6] Moreover, excluding these patients from disease-modifying OA drug (DMOAD) trials may benefit the quest for discovery of tissue structure modifying medication accompanied by analgesic activity as requested by European Medicines Agency (EMA) and Food and Drug Administration (FDA).[13 14]

Although definite NP requires an objective diagnostic test to confirm a lesion or disease of the somatosensory system, questionnaires like the painDETECT, assessing pain characteristics suggestive for NP, show high sensitivity and specificity to distinguish NP from non NP.[15] The painDETECT questionnaire predicts the likelihood of an NP component in patients with chronic low back pain,[16] and has widely been used in OA studies as well. A low score on the painDETECT questionnaire (≤12) means that the presence of an NP component is unlikely (<15%), while a high score (≥19) indicates that the presence of an NP component is likely (>90%).[16]

In general, OA patients with a high painDETECT score (more likely to have an NP component) also have higher scores on other pain questionnaires like Western Ontario McMaster Universities Osteoarthritis Index and Numeric Rating Scales (NRS),[17–23] hampering in this respect selection of patients.

In this study, for the first time, knee OA patients with a likely NP component (as defined by painDETECT score ≥19) and OA patients without a likely NP component (as defined by painDETECT score ≤12) were matched for knee pain levels, to compare differences in clinical characteristics. We hypothesise that knee OA patients with a likely NP component form a specific OA phenotype, without a relation between joint damage and clinical symptoms.

METHODS

Overall study population

Patients were selected from the Innovative Medicines Initiative Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) clinical cohort,[24] a 2-year follow-up study including 297 knee OA patients. The IMI-APPROACH consortium provides a broad database of OA patients and a longitudinal cohort study to combine conventional and new disease markers, to identify different OA phenotypes. The study is being conducted in compliance with the protocol, Good Clinical Practice, the Declaration of Helsinki and the applicable ethical and legal regulatory requirements (for all countries involved). All patients have received oral and written information and provided written informed consent. The present analysis used baseline data.

Identification of patients with and without a likely NP component

The painDETECT questionnaire[16] was used to identify patients with a high likelihood of an NP component. This questionnaire contains nine questions: seven questions to characterise pain, one for the pain course pattern and one for the presence or absence of radiating pain, leading to a final score ranging from −1 to 38. −1 is scored when all seven questions about pain characteristics are answered with 'never', the pain course pattern is 'persistent pain with pain attacks' and no radiation is present. In case of a score ≤12 a NP component is unlikely (<15%), whereas in case of a score ≥19 a NP component is likely (>90%).[16] In-between scores provide doubtful classification and patients with these intermediate scores are therefore left out of the current analyses.

Evaluation of joint pain

Multiple questionnaires were used to evaluate joint pain. The pain subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS)[25] and its equivalent for the hip (Hip disability and Osteoarthritis Outcome Score, HOOS)[26] consist of nine questions for pain, each scored on a 5-point scale. A normalised score is calculated where 0 means maximal pain and 100 means no pain. The Short Form 36 (SF-36) contains 36 questions and measures eight domains of health status, including bodily pain ranging from 0 to 100, where 0 means no pain and 100 mean maximal pain.[27] A NRS for pain[28] was used for both knees, both hips, both hands and the lower back. It consists of an 11 point-scale on which patients score pain from 0 (no pain) to 10 (worst imaginable pain). The Intermittent and Constant OA Pain (ICOAP) questionnaire[29] for knee and hip contains eleven questions, five for constant pain and six for intermittent pain, each question scored on a 5-point scale. A higher total score reflects more pain.

Evaluation of physical function

The Functional Index for Hand OA (FIHOA)[30] comprises ten questions, scored on a 4r-grade scale. Scores range from 0 (no difficulties) to 30 (maximal difficulties). In addition, two performance-based tests, recommended by OsteoArthritis Research Society International, were used in APPROACH. For the 30s chair-stand test (chair) patients had to stand up completely from a sitting position in the middle of a seat with feet shoulder width apart, flat on the floor, arms crossed at chest, and then sit completely. The result is the number of repetitions completed in thirty seconds. The 40m self-paced walk test (walk) records time in seconds needed to walk as quickly but as safe as possible (regular walking, no running) to a mark 10m away, return, and repeat for a total distance of 40m.

Evaluation of structural joint damage in the index knee

For each patient an index knee was selected based on American College of Rheumatology (ACR) clinical criteria.[31] If both knees fulfilled the criteria, the most painful knee was selected as the index knee. If equal, the right one was selected as the index knee. Standardised semiflexed posterior–anterior weight bearing knee radiographs were taken according to Buckland-Wright.[32] Kellgren and Lawrence (KL) grading was performed by one blinded observer. The intraobserver and interobserver correlation were both previously found to be good (>0.83),[33] and in IMI-APPROACH an intraclass correlation coefficient (ICC) of 0.88 was found (using 10% of the radiographs). Additionally, Knee Images Digital Analysis[34] was performed by one single experienced observer. Minimum Joint Space Width (minJSW) of the index knee (mm), osteophyte area (mm^2) and subchondral bone density (mm Alu Eq.) were used as radiographic parameters. Previous studies demonstrated an ICC of 0.73–0.99 for the different features.[35]

Evaluation of OA grades of other joints

Whole-body low-dose CT was performed to assess concomitant OA or degenerative disc disease (DDD) in case of intervertebral discs. Scans were evaluated using the OsteoArthritis CT (OACT) score, grading all joints on a 0–3 scale. For intervertebral discs, DDD of the two most degenerated levels of each region (cervical, thoracic, lumbal) were scored. Next to grades per joint, the OACT provides a score for total body OA, ranging from 0 to 72 (24 joints with a maximum score of 3 per joint). Kappa values for the intra-observer reliability for individual joints ranged from 0.79 to 0.95, and for inter-observer reliability from 0.48 to 0.95. ICC for the total OA body score ranged from 0.94 to 0.97 for different observers.[36]

Statistical analysis

First, all patients with a painDETECT ≥19 (NP) were matched in a 1:2 ratio to patients with a painDETECT score ≤12 (non-NP), using the MatchIt package from the R statistical package. Subjects were matched using KOOS pain (as a knee specific pain measure) and SF-36 pain (as a general pain score) based on the 'nearest neighbour' principle as well as using a calliper for KOOS pain (as the primary matching criterion) of ten points. These matching variables were chosen because they are known to have a significant relation with painDETECT scores.[17 20–23] Further analyses were performed using IBM SPSS Statistics V.26.0.0.1. Differences between patients with a likely NP component and matched patients without a likely NP component were evaluated using Student's t-tests (for continuous variables), and chi-squared or Fisher's Exact test when assumptions for chi-squared were not met. P<0.05 were considered statistically significant.

RESULTS

Patient characteristics

In the whole cohort of 297 knee OA patients, 24 patients (8.2%) scored ≥19 on the painDETECT questionnaire at time of inclusion, whereas 220 patients (74.8%) scored ≤12. Fifty (17.0%) patients had an in-between score (three patients did not have a painDETECT score at baseline). The characteristics of patients with a likely NP component (NP, n=24), and the matched patients without a likely NP component (non-NP, n=48) are shown in table 1. No statistically significant differences were found between groups for demographics or the matching variables (as expected). Characteristics of all patients without a likely NP component, and those with an in-between painDETECT score (13–18) are shown in

Table 1 Participant characteristics

	NP (n=24)	Non-NP (n=48)	P value
Demographics			
Age (years), mean (SD)	64.5 (6.9)	65.7 (7.3)	0.491
BMI, mean (SD)	30.7 (5.9)	29.1 (6.2)	0.295
Female, n (%)	20 (83%)	38 (79%)	0.761*
Matching variables			
KOOS pain, mean (SD)	50.8 (15.1)	49.8 (13.1)	0.777
SF-36 pain, mean (SD)	34.1 (22.8)	39.8 (16.8)	0.285

*Fisher's exact test.
BMI, body mass index; KOOS, Knee injury and Osteoarthritis Outcome Score; non-NP, matched controls; NP, neuropathic pain; SF-36, Short form 36.

Table 2 Radiographic damage in NP and non-NP patients

	NP (n=24)	Non-NP (n=48)	P value
Radiography			
KL grade, n (%)*			**0.003**
0	8 (33.3)	4 (8.3)	
1	8 (33.3)	11 (22.9)	
2	8 (33.3)	19 (39.6)	
3	0 (0)	13 (27.1)	
4	0 (0)	1 (2.1)	
minJSW (mm), mean (SD)	3.0 (1.0)	2.1 (1.4)	0.002
Osteophyte area (mm^2), mean (SD)	12.7 (11.1)	25.5 (19.1)	0.001
Mean subchondral bone density (mm Alu. Eq), mean (SD)	30.1 (4.3)	32.4 (4.7)	0.037

Statistical significant p-values are given in bold.
*Fisher's exact test.
mm Alu Eq.; mm aluminium equivalent.KL grade, Kellgren and Lawrence grade; minJSW, minimum Joint Space Width; NP, neuropathic pain.

online supplemental table 1. These two groups showed statistically significantly different KOOS pain and SF-36 pain scores compared with the NP group.

Differences in radiographic joint damage in patients with and without a likely NP component

Differences in radiographic parameters of the index knee between patients with and without a likely NP component (matched for KOOS and SF-36 pain) are shown in table 2. Patients with a likely NP component have statistically significantly less radiographic damage in their index knee (KL grade p=0.003; minJSW 3.0 vs 2.1, p=0.002; osteophyte area 12.7 vs 25.5, p=0.001; subchondral bone density 30.1 vs 32.4, p=0.037).

Differences in physical function in patients with and without a likely NP component

Differences in physical function between patients with and without a likely NP component are shown in table 3. Patients with a likely NP component have statistically significant worse hand function (FIHOA 12.3 vs 5.3, p<0.001), and perform worse on both performance-based tests (Chair test 7.3 vs 9.7, p<0.001; Walk test 38.1 vs 29.5, p=0.003).

Table 3 Physical function in NP and non-NP patients

	NP (n=24) Mean (SD)	Non-NP (n=48) Mean (SD)	P value
Physical function			
FIHOA	12.3 (6.9)	5.3 (6.3)	**<0.001**
Chair (no standing up)	7.3 (2.2)	9.7 (3.2)	**<0.001**
Walk (s)	38.1 (12.1)	29.5 (8.2)	**0.003**

Statistical significant p-values are given in bold.
FIHOA, Functional Index for Hand OsteoArthritis; NP, neuropathic pain.

Table 4 Pain scores in NP and non-NP patients

	NP (n=24) Mean (SD)	Non-NP (n=48) Mean (SD)	P value
Index knee			
ICOAP knee	13.0 (8.7)	10.5 (9.1)	0.252
NRS index knee	6.3 (2.4)	6.6 (2.2)	0.680
Contralateral knee			
NRS contralateral knee	5.8 (2.5)	4.0 (2.8)	**0.012**
Hips			
HOOS pain	61.0 (24.2)	82.8 (20.9)	**0.001**
ICOAP hip	16.8 (10.1)	6.7 (9.0)	**<0.001**
NRS left hip	4.5 (3.1)	1.9 (2.7)	**0.001**
NRS right hip	5.0 (3.1)	1.5 (2.6)	**<0.001**
Hands			
NRS left hand	6.4 (2.4)	3.9 (3.2)	**0.001**
NRS right hand	6.5 (2.4)	3.7 (3.1)	**<0.001**
Lower back			
NRS lower back	5.6 (3.4)	4.4 (3.2)	0.343

Statistical significant values are given in bold.
HOOS, Hip disability and Osteoarthritis Outcome Score; ICOAP, Intermittent and Constant Osteoarthritis Pain; NP, neuropathic pain; NRS, Numeric Rating Scale.

Differences in generalised joint pain between patients with and without a likely NP component

Differences in pain in joints other than the index knee between patients with and without a likely NP component are shown in table 4. As anticipated based on the matching process, ICOAP knee and NRS of the index knee did not differ between groups. In contrast, OA patients with a likely NP component had statistically significantly more pain in the contralateral knee (NRS 5.8 vs 4.0, p=0.012), hips (HOOS 61.0 vs 82.8, p=0.001; ICOAP hip 16.8 vs 6.7, p<0.001; NRS left hip 4.5 vs 1.9, p=0.001; NRS right hip 5.0 vs 1.5, p<0.001) and hands (NRS left hand 6.4 vs 3.9, p=0.001; NRS right hand 6.5 vs 3.7, p<0.001). Also, NRS lower back was higher, although not statistically significant (p=0.343).

Differences in OACT grades of other joints between patients with and without a likely NP component

Differences in OACT grades between patients with and without a likely NP component are shown in table 5. The OACT grade of the index knee in patients with a likely NP component was lower compared with patients without a likely NP component, indicating less joint damage and supporting the data of the standard measurements in table 2. OACT grading of other joints did not differ

Table 5 Osteoarthritis CT grades in NP and non-NP patients

	NP (n=24)	Non-NP (n=48)	P value
OACT grades			
Index knee n (%)			**0.010***
0	7 (29.2)	4 (8.3)	
1	9 (37.5)	10 (20.8)	
2	7 (29.2)	22 (45.8)	
3	1 (4.2)	12 (25.0)	
Contralateral knee n (%)			0.199*
0	4 (16.7)	4 (8.3)	
1	14 (58.3)	20 (41.7)	
2	5 (20.8)	16 (33.3)	
3	1 (4.2)	8 (16.7)	
Index patellofemoral n (%)			0.409
0	6 (25.0)	6 (12.5)	
1	10 (41.7)	18 (37.5)	
2	3 (12.5)	12 (25.0)	
3	5 (20.8)	12 (25.0)	
Contralateral patellofemoral n (%)			0.329
0	7 (14.6)	7 (29.2)	
1	9 (37.5)	15 (31.3)	
2	4 (16.7)	14 (29.2)	
3	4 (16.7)	12 (25.0)	
Left hip n (%)			0.638*
0	16 (66.7)	31 (64.6)	
1	7 (29.2)	16 (33.3)	
2	1 (4.2)	0 (0.0)	
3	0 (0.0)	1 (2.1)	
Right hip n (%)			0.868*
0	14 (58.3)	28 (58.3)	
1	7 (29.2)	16 (33.3)	
2	3 (12.5)	4 (8.3)	
3	0 (0.0)	0 (0.0)	
Left ankle n (%)			0.268*
0	21 (87.5)	33 (68.8)	
1	3 (12.5)	13 (27.1)	
2	0 (0.0)	0 (0.0)	
3	0 (0.0)	0 (0.0)	
Right ankle n (%)			0.420*
0	20 (83.3)	31 (64.6)	
1	4 (16.7)	13 (27.1)	
2	0 (0.0)	2 (4.2)	
3	0 (0.0)	0 (0.0)	

Continued

Table 5 Continued

	NP (n=24)	Non-NP (n=48)	P value
Left acromioclavicular n (%)			0.705*
0	11 (45.8)	16 (33.3)	
1	5 (20.8)	14 (29.2)	
2	2 (8.3)	3 (6.3)	
3	6 (25.0)	15 (31.3)	
Right acromioclavicular n (%)			**0.023**
0	11 (45.8)	7 (14.6)	
1	6 (25.0)	13 (27.1)	
2	1 (4.2)	8 (16.7)	
3	6 (25.0)	20 (41.7)	
Left glenohumeral n (%)			0.480*
0	21 (87.5)	36 (75.0)	
1	2 (8.3)	10 (20.8)	
2	1 (4.2)	1 (2.1)	
3	0 (0.0)	0 (0.0)	
Right glenohumeral n (%)			0.340*
0	19 (79.2)	38 (79.2)	
1	2 (8.3)	8 (16.7)	
2	3 (12.5)	2 (4.2)	
3	0 (0.0)	0 (0.0)	
C1 n (%)			0.786*
0	1 (4.2)	2 (4.2)	
1	5 (20.8)	7 (14.6)	
2	7 (29.2)	11 (22.9)	
3	11 (45.8)	28 (58.3)	
C1 facet n (%)			0.943
0	3 (12.5)	6 (12.5)	
1	5 (20.8)	11 (22.9)	
2	6 (25.0)	9 (18.8)	
3	10 (41.7)	22 (45.8)	
C2 n (%)			0.083
0	6 (25.0)	8 (16.7)	
1	3 (12.5)	12 (25.0)	
2	10 (41.7)	9 (18.8)	
3	5 (20.8)	19 (39.6)	
C2 facet n (%)			0.676
0	8 (33.3)	15 (31.3)	
1	7 (29.2)	9 (18.8)	
2	3 (12.5)	10 (20.8)	
3	6 (25.0)	14 (29.2)	
T1 n (%)			0.422
0	0 (0.0)	0 (0.0)	
1	4 (16.7)	15 (31.3)	
2	10 (41.7)	19 (39.6)	
3	9 (37.5)	14 (29.2)	

Continued

Table 5 Continued

	NP (n=24)	Non-NP (n=48)	P value
T1 facet n (%)			0.705*
0	10 (41.7)	25 (52.1)	
1	8 (33.3)	10 (20.8)	
2	4 (16.7)	8 (16.7)	
3	2 (8.3)	5 (10.4)	
T2 n (%)			0.334*
0	1 (4.2)	1 (2.1)	
1	7 (29.2)	24 (50.0)	
2	11 (45.8)	15 (31.3)	
3	4 (16.7)	8 (16.7)	
T2 facet n (%)			0.916*
0	16 (66.7)	28 (58.3)	
1	5 (20.8)	13 (27.1)	
2	3 (12.5)	6 (12.5)	
3	0 (0.0)	1 (2.1)	
L1 n (%)			**0.042***
0	2 (8.3)	5 (10.4)	
1	2 (8.3)	13 (27.1)	
2	13 (54.2)	11 (22.9)	
3	6 (25.0)	18 (37.5)	
L1 facet n (%)			0.277*
0	14 (58.3)	16 (33.3)	
1	3 (12.5)	12 (25.0)	
2	1 (4.2)	5 (10.4)	
3	5 (20.8)	14 (29.2)	
L2 n (%)			0.772
0	5 (20.8)	15 (31.3)	
1	7 (29.2)	15 (31.3)	
2	8 (33.3)	12 (25.0)	
3	3 (12.5)	5 (10.4)	
L2 facet n (%)			0.357*
0	18 (75.0)	31 (64.6)	
1	5 (20.8)	8 (16.7)	
2	0 (0.0)	3 (6.3)	
3	0 (0.0)	5 (10.4)	
Total body score, mean (SD)	25.4 (8.4)	29.9 (9.0)	**0.044**

Statistical significant p-values are given in bold.
*Fisher's exact test.
NP, neuropathic pain; OACT, OsteoArthritis CT.

between both groups, except for the right acromioclavicular joint (p=0.023; less damage in NP group), and the worst degenerated intervertebral disc of the lumbal spine (p=0.042; more damage in NP group).

DISCUSSION

In the IMI-APPROACH knee OA cohort 24 patients out of 297 (8%) had a likely NP component. Interestingly, despite similar general knee pain levels (due to matching), patients with a likely NP component had less radiographic damage in their index knee, but a significant more impaired physical function. This might be explained by higher pain scores in joints other than the index knee, although OACT grades of these joints did not statistically significantly differ between patients with and without an NP component. The total body OACT score was even lower in patients with a likely NP component. These data indicate that patients with a likely NP component, determined with the painDETECT questionnaire, represent a specific phenotype, where local and overall joint damage is not the main cause of pain and disability.

Although questionnaires like the painDETECT show high sensitivity and specificity to distinguish NP from non-NP,[15] an objective measurement to show presence of a lesion of the somatosensory system is required, which has not been done within IMI-APPROACH. As a consequence, other pain mechanisms than a pure NP component, such as nociplastic pain or occurrence of central sensitisation may play a role in these patients as well. Although fibromyalgia patients were excluded from inclusion in the IMI-APPROACH cohort, the presence of comorbidities/generalised pain syndromes was only assessed by asking the patients directly at time of inclusion. Objective scoring to determine specific pain syndromes was not used. Therefore, the presence of other pain phenotypes cannot be excluded.

The majority of the patients with a likely NP component (67%) had KL grade of 0 or 1. This raises the question whether these subjects are actually knee OA patients. The patients of the IMI-APPROACH knee OA cohort were included based on the clinical ACR criteria for knee OA. The agreement between these criteria and symptomatic radiographic knee OA is known to be low.[37] The IMI-APPROACH also did use a knee radiograph, taken at a screening visit, for final selection of patients, which was afterwards scored for KL grading performed by one observer blinded for the source of material. In the whole cohort, 47% of patients had a KL grade of 0 or 1 at baseline. The follow-up data of the study are currently being analysed and will demonstrate whether these patients are actual knee OA patients.

In our study, 8% of patients reported a painDETECT score ≥19. The presence of painDETECT scores ≥19 in knee OA patients in other studies ranges from 5% to 67%.[17–22 38 39] In a recently published systematic review, a prevalence of 19% (95% CI 15% to 24%) in patients with hip and knee OA was found, although the prevalence depended on population type: community based 17% (95% CI 11% to 24%), hospital based 25% (95% CI 15% to 36%), RCT patients 15% (95% CI 5% to 26%), end-stage knee OA 16% (95% CI 8% to 26%).[40] In the general population these numbers ranged from 1% to 14%.[41–43]

In our study, patients with a likely NP component showed less radiographic damage compared to patients without a likely NP component that were matched for

KOOS and SF-36 pain. Others compared patients with clinical knee OA with and without an NP component and found no differences in duration of OA symptoms,[44] refuting the argument of NP being simply a symptom of OA progression. Duration of the OA was not assessed in the IMI-APPROACH study, irrespectively, it supports the concept of OA patients with a likely NP component as a specific phenotype, not related to radiographic severity (our data) or duration[44] of disease.

Age, body mass index (BMI) and gender did not differ between patients with and without a likely NP component, confirming results from previous studies.[19 22] However, in other studies OA patients with higher painDETECT scores were younger[44] and had a higher BMI.[18 44] In contrast to our study, these studies included patients with painDETECT scores from 13 to 18 (uncertain result) in their analysis, giving a possible explanation for the different results.

In our study, patients with a likely NP component had a worse self-reported hand function (FIHOA) and worse outcomes on the two performance-based tests compared with patients without a likely NP component. Others also found OA patients with NP-like symptoms had impaired walk and stair climb activity,[21] but no difference in sit-to-stand activity.[17 21] Self-reported joint related function is also diminished in knee OA patients with a likely NP component compared with patients without a likely NP component.[17 18] Possibly, the impaired function is caused by OA pain in other joints. Indeed, more pain was found in the other joints, something that was also found previously.[20] However, joint damage of joints other than the index knee, assessed by OACT grades, did not differ between both groups. The total body score was even lower in patients with a likely NP component compared with patients without a likely NP component. Nevertheless, increased lumbar spine damage in patients with a likely NP component could contribute to the worse results on the two performance-based tests. Although, this does not explain the observed limited hand function. Besides, NRS pain of the lower back did not statistically differ between both groups. In addition to more severe overall pain, other causes for the physical impairment should be considered as well. Psychosocial factors, less physical activity and other comorbidities are factors known to interfere with pain and physical impairment.[45]

In agreement with the above-mentioned finding that in patients with a likely NP component local joint damage is not the main cause of pain (similar pain level but less radiographic joint damage), these findings show that this is the case for other joints as well (more pain but comparable joint damage).

Based on our results, it is possible that the generally found discordance between radiographic damage and pain in OA studies, is explained by the inclusion of patients with an NP component. Online supplemental table 2 shows that the relationships between knee pain and radiographic damage are very small in the whole IMI-APPROACH. Excluding patients with a likely NP component from this cohort, increases the relationships. The relationships increased even more when patients with an in-between painDETECT score (13–18) were also excluded. These data indicate that OA patients with a likely NP component indeed weaken the relationship between joint damage and pain.

Clearly, in OA patients with a likely NP component, joint damage itself is not the driving factor of pain and loss of function. This implies that pain and physical function are less likely to improve after TKA in this specific group. In general, about 20% of TKA is not successful.[46] Indeed, multiple studies found that OA patients with a likely NP component were twice as likely to experience pain after TKA than those without a likely NP component.[47–49] This effect may also interfere in case of DMOAD trials where the combination of tissue structure modification and pain control is needed (as requested by EMA and FDA[13 14]).

Obviously, the small number of patients with a NP component (n=24) is a clear limitation of this study. The main objectives of the IMI-APPROACH cohort study did not include evaluation of an NP component, therefore, the current analysis should be considered as post-hoc analysis with limited power. Nevertheless, the results are important to consider in patient selection of future OA clinical trials and further research to characterise this specific group is warranted.

In conclusion, this study shows that OA patients with a likely NP component possibly reflect an OA phenotype where local tissue damage is not the leading cause for pain and physical impairment. As a consequence, the general one-size fits all approach, focused on treatment of nociceptive pain (resulting from tissue damage), might be inappropriate in this specific patient group. Therefore, it is advised to use the painDETECT questionnaire, or an alternative measure to assess NP. Identifying these OA patients and offering them a more personalised treatment[6 15] as well as excluding them from DMOAD trials could increase successes.

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