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a pre-defined ancillary analysis from a randomized controlled trial

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The efficacy of non-surgical treatment on pain and sensitization in patients with knee osteoarthritis: a pre-defined ancillary analysis from a randomized controlled trial

INTRODUCTION

Pain associated with knee osteoarthritis (OA) is recognized as a complex phenomenon encompassing several mechanisms\(^1\), indicating that its assessment\(^2\) and treatment\(^3\) should be multimodal to target all co-responsible mechanisms. Pain intensity, usage of pain medication, pain pattern and spreading of pain are important pain-related measures\(^2,4,5\). Another pain mechanism known to be important in patients with advanced knee OA is sensitization\(^4,6,7\), defined as increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs\(^8\).

Quantitative sensory testing (QST) can be used to assess sensitization in patients with knee OA using a mechanism-based approach\(^3\). By assessing the somatosensory response evoked by applying controlled noxious or innocuous stimuli (e.g. using a pressure algometer) it is possible to quantify the sensitization of a patient\(^9\). Compared to healthy controls, pressure pain sensitivity found locally at the affected knee (and adjacent body parts) in patients with chronic pain can be associated with peripheral and/or central sensitization, while pressure pain sensitivity distantly from the knee may reflect generalized central sensitization (spreading sensitization) only\(^4,9\). Both peripheral and spreading sensitization have previously been demonstrated in patients with knee OA compared to pain-free controls\(^6,10-14\), although they have mostly been investigated in more advanced knee OA. Evidence regarding sensitization in patients with less advanced knee OA is scarce.

While the evidence concerning the efficacy of non-surgical treatment on knee OA pain is strong\(^15,16\), less attention has been paid to its efficacy on sensitization processes\(^17,18\). Two previous studies have assessed the effects of exercise on sensitization in knee OA, but with conflicting results\(^13,19\).
Henriksen et al.\textsuperscript{19} demonstrated that 12 weeks of supervised exercise reduced pressure pain sensitivity compared to a no-attention control group, while Kosek et al.\textsuperscript{13} found that exercise (average duration of 12 weeks) had no effect on pressure pain sensitivity. Furthermore, no studies have investigated the combined efficacy of the recommended treatments in reducing both pain and sensitization even though this could improve outcome\textsuperscript{18}.

A previously published\textsuperscript{20} randomized controlled trial (RCT) showed that a 3-month treatment program of neuromuscular exercise, education, diet, insoles and pain medication (the MEDIC-treatment) resulted in greater long-term improvements in pain, function and quality of life outcomes compared to information and treatment advice (usual care) in patients with knee OA not eligible for total knee replacement (TKR). The aim of this pre-specified ancillary analysis was to investigate the efficacy of the MEDIC-treatment to improve different pain-related measures (pain intensity, pain location and pattern, spreading of pain and usage of pain medication) and sensitization after 3 months compared to usual care.

We hypothesized that the MEDIC-treatment would result in greater improvements in the pain-related measures and sensitization than usual care at 3-month follow-up.

\section*{METHOD}

\subsection*{Study design}

This was an ancillary analysis of the 3-month results from a two-arm parallel group assessor-blinded RCT (1:1 treatment allocation) conforming to the CONSORT statement for reporting RCTs\textsuperscript{21}. The current analyses were pre-defined in the statistical analysis plan (made available before unblinding the data)\textsuperscript{22}. 
All details of the recruitment process, full eligibility criteria, the process of randomization, allocation concealment and detailed description of the intervention have been published previously.23

**Patients**

One hundred patients with radiographic and symptomatic knee OA found not eligible for TKR by an orthopedic surgeon, but experiencing more than mild limitations, were enrolled. Patients were recruited from two specialized, public outpatient clinics at Aalborg University Hospital (Frederikshavn and Farsoe, 50 patients from each clinic) between 3 April 2012 and 12 July 2013. Major exclusion criteria were scores above 75 in the self-report questionnaire Knee Injury and Osteoarthritis Outcome Score (KOOS), defined as the average score for the subscale scores for pain, symptoms, activities of daily living (ADL) and quality of life (QOL), previous ipsilateral knee replacement and mean knee pain in the previous week greater than 60 mm on a 0–100 mm visual analogue scale (VAS).

All patients gave informed consent before being enrolled, and the study was conducted in accordance with the Helsinki declaration and approved by the local Ethics Committee of The North Denmark Region (N-20110085). Furthermore, this ancillary study was registered at ClinicalTrial.gov (NCT02091830).

**Intervention**

**The MEDIC-treatment**

The 3-month MEDIC-treatment consisted of prescribing education, exercise and insoles to everyone in the MEDIC group, while weight loss and/or pain medication were prescribed if
indicated. The treatment was given at Aalborg University Hospital, Denmark, by physiotherapists and dieticians trained in providing the treatment to ensure standardization of the treatment program.

**Education**

Two 60-min sessions of education focusing on disease characteristics, OA pain and how to control and monitor it during exercise, treatment and help to self-help by actively engaging the patients.

**Exercise**

The MEDIC group participated in The NEuroMuscular EXercise training program (NEMEX), previously found feasible in patients with moderate to severe knee OA, twice weekly with each session lasting 60 min. The program is based on neuromuscular and biomechanical principles with different levels of difficulty for each exercise. To improve long-term adherence, the exercise program was followed by a transition period of 8 weeks to gradually accustom the patients to continue exercising at home.

**Dietary advice**

If patients had a body mass index (BMI) $\geq 25$ at baseline, they underwent a dietary weight loss program based on principles from motivational interviewing, with instructions and advice related to the readiness of the individual patient to change dietary habits and take action. It consisted of four 60-min sessions, with the aim of reducing body weight by at least 5%.

**Insoles**

A set of individually fitted full-length Formthotics System insoles with medial arch support (Foot Science International, Christchurch, New Zealand) was given to the patients. Patients with a knee knee-lateral-to-foot position (the knee moves over or lateral to the 5th toe in three or more of five
trials of the valid and reliable single limb mini squat test\textsuperscript{27}) had a 4° lateral wedged added to their insole.

**Pain medication**

If found relevant, paracetamol 1 g four times daily, ibuprofen 400 mg three times daily, and pantoprazol 20 mg daily were prescribed. The prescription was reassessed every 3 weeks to supervise the use and indications of the medication. If the continuation of the pain medicine during the 3-week period was questioned by the patient (e.g. due to pain relief), the patients were instructed to contact the project physiotherapist.

**Usual care**

The usual care group was given two standardized information leaflets. These included information on knee OA with regard to etiology, symptoms, common functional limitations, recommended treatments and general advice on how to address the symptoms yourself and information on where in The North Denmark Region they could seek advice regarding treatment and general information on how to achieve a healthy lifestyle. The leaflets were designed to reflect current treatment of patients with knee OA in clinical practice, which has been demonstrated to be suboptimal compared to clinical guidelines\textsuperscript{28, 29}

**Outcomes**

Both the baseline and 3-month follow-up were carried out at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Denmark, by the same outcome assessor. The assessor was unaffiliated with the treatment sites, blinded to treatment allocation, and specifically trained in all aspects of the assessments.

**Assessment of pain**
Peak pain intensity in the most affected knee during the previous 24 h was assessed on a 100 mm VAS with terminal descriptors of ‘no pain’ and ‘worst pain possible’. We chose peak pain intensity since it has been frequently applied in studies on sensitization in knee OA-related pain\textsuperscript{6,7,30}. The VAS is a measure of pain widely used in patients with knee OA that is valid, reliable and responsive\textsuperscript{31}.

*Pain intensity during function*

Knee pain intensity after 30 min of walking was assessed on a 100-mm VAS with terminal descriptors of ‘no pain’ and ‘worst pain possible’. Pain intensity after 30 min of walking was chosen, since it can serve as an indirect measure of how knee pain affects function.

*Knee pain location and pattern*

Knee pain location and pattern in the most affected knee were assessed using the reliable interviewer-administered questionnaire Knee Pain Map previously applied in patients with knee OA\textsuperscript{5}. The Knee Pain Map identifies painful areas of the knee and characterizes the pain as localized, regional or diffuse\textsuperscript{5}. Since diffuse pain is indicative of a more progressed sensitization\textsuperscript{4}, the pain location and pattern were dichotomized (diffuse pain in the most affected knee yes/no).

*Spreading of pain*

The patients were asked to shade body sites with pain in the previous 24 hours on a region-divided body chart (26 sites in total). The number of pain sites was applied to classify the spreading of pain as previously suggested in a large-scale study on multisite pain\textsuperscript{32}.

*Usage of pain medication*
This was defined as any pain medication taken on a regular basis during the last week at baseline and at the 3-month follow-up. The results were dichotomized (pain medication yes/no) due to non-uniformity of the distribution of pain medication intake.

**Assessment of sensitization**

Pressure pain thresholds (PPTs) were measured bilaterally using a handheld algometer with a 1 cm² probe (Algometer Type II, Somedic AB, Hoerby, Sweden). The pressure was applied perpendicular to the skin at a constant rate of 30 kPa/s until the patient felt the pressure change to pain and pressed a button defining the PPT. One or two test assessments were performed at the dorsal aspect of the hand to ensure that the patient understood the procedure. The test procedure has previously been assessed in a test-retest reliability and agreement study with 20 patients with knee OA that demonstrated intraclass correlation coefficients (2-way random-effects model, consistency-type) and 95% limits of agreement (95% LOA; presented as the difference between the mean difference and the upper and lower LOA) ranging from 0.84 to 0.91 and 199.6 to 434.0 kPa for the different sites. The 95% LOA corresponds to the minimal detectable change (MDC) for the assessment method.

**Localized sensitization**

Localized sensitization (peripheral sensitization) was assessed using PPTs from four sites at the knee, all in proximity to the patella: (1) 3 cm medial to the midpoint of the medial edge, (2) 2 cm proximal to the midpoint of the superior edge, (3) 3 cm lateral to the midpoint of the lateral, and (4) at the centre. PPTs were obtained twice at each site, and the mean of all four sites was used in the analyses.

**Spreading sensitization**
Spreading sensitization (central sensitization) was assessed using PPTs from the tibialis anterior muscle (lower leg: 5 cm distal to the tibial tuberosity), and the extensor carpi radialis longus muscle (forearm: 5 cm distal to the lateral epicondyle of the humerus). PPTs were obtained twice at each site, and the means for the lower leg and for the forearm were used in the analyses.

Statistical analysis

Sample size

The sample size was calculated based on the pre-defined primary hypothesis regarding peak pain intensity. The sample size needed to detect a 10-point difference (SD 14) between groups in peak pain intensity was 41 patients in each group (power of 90% and a significance level at 0.05 (2-sided)). To account for any TKRs performed during follow-up and for missing data, the dropout rate was set to 20%, and a total of 100 patients were randomized. Due to the ancillary nature of this pre-specified analysis, the sample size was deemed adequate for providing additional characterization of the effects of the MEDIC-treatment.

Ancillary analyses

Since this was an ancillary analysis, only patients (not undergoing a TKR) with available data from both the baseline and 3-month follow-up were included in the analyses. No adjustments for multiplicity were done as endorsed by The European Agency for the Evaluation of Medicinal Products when ancillary analyses are declared as supportive.

A Student’s t-test was used to evaluate change in pain intensity and number of pain sites between and within groups. A 3-way analysis of variance (ANOVA) was used to evaluate change in PPT from baseline to 3 months using the fixed factors group (MEDIC, usual care), site (knee, lower leg and forearm) and side (most affected, contralateral). The analysis was conducted both unadjusted
and adjusted (baseline PPT, gender and age). Within-group changes in PPTs due to the treatment were further assessed using repeated measures ANOVA with time (baseline, 3 months) as the within-subject factor and site (knee, lower leg and forearm) and side (most affected, contralateral) as the between-subject factors for both the MEDIC group and the usual care group. The assumption of homogeneity of variance was tested using Levene’s test (P > 0.05), and the assumption of normal distribution was tested by visual inspection of Q-Q plots. If findings were non-significant, a sensitivity-analysis was performed that included only those participating in at least 75% of the exercise sessions. Tukey-Kramer was used as a post hoc test if ANOVA factors or interactions were significant.

The relative risks for usage of pain medication and diffuse pain were estimated and compared between groups using a Poisson regression model with a robust error variance for the confidence intervals.

The significance level was set at P < 0.05, and all analyses were performed in either IBM SPSS Statistics (Version 22, IBM Corporation, Armonk, NY, USA) or Stata 13 (StataCorp, College Station, TX, USA).

RESULTS

In all, 654 patients seen in secondary care by an orthopedic surgeon were assessed for eligibility, 553 were excluded, and one was not willing to undergo randomization. The primary reasons for exclusion were being eligible for a TKR (n = 192), no radiographic OA (Kellgren-Lawrence score < 1; n = 87), and inability to comply with the study protocol (n = 159). One hundred patients were randomized, with 43/50 (86%; one patient underwent TKR during the 3 months) in the MEDIC group and 46/50 (92%) in the usual care group completing both baseline and 3-month follow-up.
For further information on the study flow, please refer to\textsuperscript{20}. Patient characteristics of the groups at baseline are presented in Table 1 and pain location and pattern at baseline are presented in Table 2.

**Between-group analyses**

**Peak pain intensity**

There was a statistically significant difference in change (95 % CI) from baseline to 3 months of 15.4 (2.6 to 28.2) in peak pain intensity (P = 0.019), favoring the MEDIC group.

**Pain intensity during function**

There was a statistically significant difference in change (95% CI) from baseline to 3 months of 32.6 (18.1 to 45.0) in pain intensity after 30 min of walking (P < 0.001) favoring the MEDIC group.

**Knee pain location and pattern**

There was no significant difference between groups in the number of patients with diffuse pain at 3 months compared to baseline.

**Spreading of pain**

There was a statistically significant difference in change (95% CI) from baseline to 3 months of 0.86 (0.03 to 1.70) in number of sites with pain (P = 0.042), favoring the MEDIC group.

Figure 1 illustrates the difference in body sites with pain at baseline and after 3 months in the MEDIC group and the usual care group.

**Usage of pain medication**

There was no significant difference between groups in the usage of pain medication at 3 months compared to baseline.
Localized and spreading sensitization

No statistical difference in change in PPTs from baseline to 3 months was found between groups in the crude analysis ($F(1,468) = 0.028, P = 0.868$) or when adjusting for baseline PPT, age and gender ($F(1,465) = 0.015, P = 0.902$; Fig. 2). Including only those participating in at least 75% of the exercise sessions in the MEDIC group still demonstrated no statistical difference in change in PPTs from baseline to 3 months between groups ($F(1,366) = 0.585, P = 0.445$).

Within-group analyses

Within-group results are presented in Tables 3–5.

DISCUSSION

This study showed that a 3-month non-surgical treatment program was associated with greater improvements in outcome with regard to pain intensity and spreading of bodily pain, but not sensitization, knee pain pattern and usage of pain medication after 3 months compared to information and treatment advice in patients with knee OA not eligible for TKR. These findings confirm that pain has a multitude of facets, and that treatment results may differ depending on what pain-related measures are evaluated. This is the first study evaluating multiple pain-related measures, including sensitization, in a randomized setting in patients with knee OA.

Comparison to previous studies on pain

We demonstrated large between-group differences with regard to change in pain intensity from baseline to 3 months, confirming previous RCTs on the efficacy of a non-surgical treatment program in reducing pain in patients with knee OA\textsuperscript{35, 36}. Furthermore, our study extends these findings by adhering to the recommendation that other aspects of the complexity of pain than pain intensity alone should be addressed\textsuperscript{2}, thus giving a broad perspective on the effects of a non-surgical
treatment program in patients with knee OA. In addition to improvements in pain intensity, we demonstrated that the MEDIC group had a larger reduction in the number of body sites with pain following the treatment as compared with the usual care group and a within-group reduction in the proportion using pain medication. This could be related to systemic anti-inflammatory effects from exercise that have previously been suggested to be the reason for the protective effects of exercise on cardiovascular disease and type 2 diabetes\textsuperscript{37} and improvements in well-being and other psychosocial components that have been demonstrated to result from exercise\textsuperscript{38}. Furthermore, education, i.e. teaching the patient about the etiology of the pain and how to deal with it, is known to be effective in the treatment of chronic musculoskeletal pain\textsuperscript{39}, thereby offering an additional explanation for the findings. Either way, the reduction of total body sites with pain as a result of non-surgical treatment of the knee is promising because musculoskeletal pain has been suggested to spread over time\textsuperscript{4}, and because having pain elsewhere is significantly associated with persistent pain after joint replacement \textsuperscript{40-42}. A recent study applying the same region-divided body chart that we used demonstrated that patients with chronic knee pain after revision TKR (all undergoing their primary TKR due to knee OA) had a mean of six body sites with pain and a mean pain duration of approx. 14 years\textsuperscript{43}, while the patients in our study had a mean of three body sites with pain and only 28\% of the patients had had knee pain for more than 10 years. Even though a direct linkage between the spreading of pain and the duration cannot be established based on cross-sectional data, these results offers some support to the proposition that pain will become widespread over time if not treated properly\textsuperscript{4} This notion is further supported by a prospective study by Andersen et al.\textsuperscript{44} showing that chronic pain in the knees increase the risk of developing chronic pain elsewhere over time. This highlights the potential of multimodal treatment for pain relief in patients with knee OA.

**Comparison to previous studies on sensitization**
While the previous studies investigating the efficacy of exercise on sensitization in knee OA, a RCT and a controlled before-and-after study, both included a passive control group, we advised our control group to initiate non-surgical treatment on their own, thereby resembling contemporary treatment in patients with knee OA found not eligible for TKR. In the MEDIC group of our study, the proportion with diffuse knee pain was reduced following treatment indicating an improvement in sensitization. In both groups, improvements were seen in measures reflecting localized sensitization (peripheral sensitization: PPTs from the knee) and spreading sensitization (central sensitization: PPTs from the lower leg and forearm), but we found no significant difference in sensitization between groups. Furthermore, the improvements within groups were smaller than the MDC for handheld algometry, which is why it cannot be ruled out that the lack of difference between groups was actually caused by measurement uncertainty. Differences in measurement uncertainty could also help explain the conflicting results in the two previous studies, since the study by Kosek et al. also applied a handheld algometer in the assessment of sensitization, while Henriksen et al. applied a computer-controlled cuff algometer that is less affected by measurement variability. However, it is important to recognize that the differences in PPT found by Henriksen et al. were small and of questionable clinical relevance. All together, this indicates that sensitization may not be an ideal outcome measures in trials in the general population of patients with knee OA.

Sensitization in knee osteoarthritis – only relevant for a subgroup of patients?

The so far conflicting results on the effects of non-surgical treatment on sensitization compared to the vast body of evidence supporting the effects of the same treatments on pain could potentially be explained by the presence of subgroups of OA patients with more sensitization and OA patients with less or no sensitization. Despite similar clinical pain intensities, a subgroup of patients...
with knee OA who had high local knee pain sensitivity to pressure had higher pain sensitivity to pressure at the lower leg and the forearm than those with low local knee pain sensitivity\(^7\). This highlights that subgroups with more pronounced sensitization exist within a group of patients with knee OA with similar severities of symptomatic knee OA. Subgroups may however exist even among those considered being healthy, since the variability in PPTs is large in a healthy population\(^4\). PPTs from the knee (approx. 600 kPa), lower leg (approx. 500 kPa) and forearm (approx. 350 kPa) in pain-free subjects of comparable age and gender distribution\(^6\) are similar to those demonstrated at baseline in our study. In the same study, those severely affected by sensitization had a mean knee pain intensity of 80 out of 100\(^6\), indicating a more progressed knee OA than the study population in our study (mean pain of 58 out of 100). Since knee OA pain intensity is related to the severity of the sensitization\(^6\),\(^7\),\(^12\),\(^30\),\(^49\), this suggests that the pain sensitization may not yet have developed into a clinical relevant parameter in our study population, potentially explaining the non-significant differences between groups. Targeting non-surgical treatment of sensitization towards those actually affected by the problem has the potential to desensitize the central nervous system by affecting mechanisms involved in the sensitization\(^18\).

**Limitations**

The nociceptive input in knee OA could originate from several sources, including periarticular tissues, inflammation, elevated intraosseous pressure in the subchondral bone, and elevation of periosteum by osteophyte growth\(^5\). Since the PPTs of our study were not specific to all these structures, it is unclear whether PPTs actually reflect the true pain and sensitization of the knee OA joint. However, the PPT measurement sites have been applied in several previous studies successfully differentiating between different levels of sensitization in patients with knee pain\(^6\),\(^7\),\(^12\),\(^43\). Due to the multimodal setup of the treatment program, it is unknown whether all components of the MEDIC-treatment are required for the improvements in pain outcomes, and at the same time,
the multimodal setup makes it impossible to identify the efficacy of an individual treatment modality alone. However, since the treatment program adheres to current guidelines on the treatment of knee OA\textsuperscript{15,16} and is embedded in secondary health care, the strengths of the design are considered to outweigh the limitations.

**Conclusions**

A combined treatment with neuromuscular exercise, patient education, diet, insoles and pain medication resulted in greater improvements in pain intensity and spreading of pain outcomes than usual care (information and advice) in patients with knee OA not eligible for TKR. For this patient population no differences in effect were seen on sensitization parameters, knee pain pattern and usage of pain medication after 3 months of the combined treatment compared to usual care. This suggests that sensitization, as measured in our study, is less useful as an outcome measure in trials of the general knee OA population.

**ACKNOWLEDGMENTS**

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Finally, the study funders and patients participating should be acknowledged, without their participation the trial would not have been possible to conduct.

**AUTHOR CONTRIBUTIONS**

**Study conception and design.** Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen

**Acquisition of data.** Skou.

**Analysis and interpretation of data.** Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen.

**Drafting the article or revising it critically for important intellectual content.** Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen

**Final approval of the article.** Skou, Roos, Laursen, Rathleff, Arendt-Nielsen, Simonsen, Rasmussen

All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**DECLARATION OF FUNDING AND ROLE OF THE FUNDING SOURCE**

This trial is partially funded by The Danish Rheumatism Association and The Association of Danish Physiotherapists Research Fund. The funders did not have any role in this study other than to provide funding.

**CONFLICT OF INTEREST**

None declared.
ETHICS

Ethics approval was obtained for the randomized controlled trial from the local Ethics Committee of The North Denmark Region (N-20110085), the participants gave informed consent to participate, and the trials were conducted in accordance with the Helsinki declaration. The trial was also registered at ClinicalTrial.gov (NCT01535001).
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FIGURE LEGENDS

Figure 1. Pressure pain thresholds on the most affected side. Mean pressure pain thresholds (PPT) measured in kPa using a handheld algometer on the knee, lower leg and forearm. No between-group differences were found, while significantly higher PPTs (*; P < 0.05) were found for all sites on both the most affected and contralateral side after 3 months in both the MEDIC group and the usual care group. Error bars indicate 95% confidence intervals.

Figure 2. Pain sites. Sites of the body where at least 10% of the patients in the MEDIC group (A) and in the usual care group (B) reported pain during the previous 24 hours. A black shade indicates that at least 10% reported pain at both baseline and at the 3-month follow-up, while a grey shade indicates that at least 10% reported pain at baseline, but not at the 3-month follow-up. The right side of the body in the figures has been set as the side mostly affected by knee osteoarthritis.
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>MEDIC</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women, n (%)</td>
<td>26 (52)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>64.8 (8.7)</td>
<td>67.1 (9.1)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)</td>
<td>30.6 (5.6)</td>
<td>29.4 (5.2)</td>
</tr>
<tr>
<td>Study knee, n right (%)</td>
<td>18 (36)</td>
<td>27 (54)</td>
</tr>
<tr>
<td>Bilateral knee pain, n (%)</td>
<td>18 (36)</td>
<td>21 (42)</td>
</tr>
<tr>
<td>Duration of knee symptoms, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>6–12 months</td>
<td>9 (18)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>1–2 years</td>
<td>10 (20)</td>
<td>5 (10)</td>
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<tr>
<td>2–5 years</td>
<td>11 (22)</td>
<td>13 (26)</td>
</tr>
<tr>
<td>5–10 years</td>
<td>4 (8)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>More than 10 years</td>
<td>12 (24)</td>
<td>16 (32)</td>
</tr>
<tr>
<td>Radiographic knee OA severity (Kellgren-Lawrence), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>7 (14)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>13 (26)</td>
<td>15 (30)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>13 (26)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>17 (34)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Peak pain intensity in the previous 24h (0–100), mean (SD)</td>
<td>60 (23)</td>
<td>56 (25)</td>
</tr>
<tr>
<td>Pain intensity after 30 min walking (0–100), mean (SD)</td>
<td>62 (26)</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Have used pain medication in the last week, n (%)</td>
<td>32 (64)</td>
<td>30 (60)</td>
</tr>
<tr>
<td>Body sites with pain, mean (SD)</td>
<td>3.2 (2.9)</td>
<td>2.8 (2.1)</td>
</tr>
</tbody>
</table>
Table 2. Pain location and pattern at baseline in the most affected knee

<table>
<thead>
<tr>
<th>Pain location and pattern, n (%)</th>
<th>MEDIC (n=49)</th>
<th>Usual Care (=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse[^1]</td>
<td>34 (69)</td>
<td>26 (55)</td>
</tr>
<tr>
<td>Regional</td>
<td>13 (27)</td>
<td>21 (45)</td>
</tr>
<tr>
<td>Medial region</td>
<td>9 (18)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Patella region</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Lateral region</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Back of knee, regional</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Localized</td>
<td>13 (27)</td>
<td>21 (45)</td>
</tr>
<tr>
<td>Superior medial</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Medial joint line</td>
<td>10 (20)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Inferior medial</td>
<td>4 (8)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Patella, local</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Superior lateral</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lateral joint line</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Inferior lateral</td>
<td>1 (2)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Back of knee, local</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

[^1]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.

[^2]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.

[^3]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.

[^4]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.

[^5]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.

[^6]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.

[^7]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.

[^8]: Of these 20 in the MEDIC group and 13 in the usual care group were classified as diffuse pain due to either >3 areas of localized pain, >2 regions of pain, and/or >1 location and 1 non-overlapping region.
**Table 3. Within-group analyses**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MEDIC group</th>
<th>Usual Care group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$F$ statistics (df) or $P$ value</td>
<td>$F$ statistics (df) or $P$ value</td>
</tr>
<tr>
<td><strong>Mean improvements</strong></td>
<td>$(95% \text{ CI})$</td>
<td>$(95% \text{ CI})$</td>
</tr>
<tr>
<td>Peak pain intensity</td>
<td>$27.9$ (18.4 to 37.5)</td>
<td>$13.4$ (4.3 to 22.5)</td>
</tr>
<tr>
<td>Pain intensity after walking</td>
<td>$34.8$ (25.0 to 44.6)</td>
<td>$2.7$ (-6.9 to 12.3)</td>
</tr>
<tr>
<td>Body sites with pain</td>
<td>$1.19$ (0.49 to 1.89)</td>
<td>$0.33$ (-0.16 to 0.81)</td>
</tr>
<tr>
<td>Pressure pain thresholds$^1$</td>
<td>$48.293$ (1, 240)</td>
<td>$31.661$ (1, 228)</td>
</tr>
</tbody>
</table>

$^1$ There was a significant interaction between time and site ($F(2,240) = 3.242$, $P = 0.041$; Fig. 1A) in the MEDIC group demonstrating that within-group changes from baseline to 3 months were larger for PPTs from the lower leg than for the knee and the forearm. No other interactions were found.
Table 4. Diffuse knee pain in the most affected knee

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MEDIC group (95% CI)</th>
<th>Usual Care group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (41, 40)</td>
<td>0.78 (0.63 to 0.88)</td>
<td>0.53 (0.37 to 0.68)</td>
</tr>
<tr>
<td>3 months (41, 40)</td>
<td>0.45 (0.31 to 0.61)</td>
<td>0.40 (0.26 to 0.56)</td>
</tr>
</tbody>
</table>

Risk ratio for having diffuse pain at 3 months vs. baseline

<table>
<thead>
<tr>
<th>Crude estimate</th>
<th>MEDIC group (95% CI)</th>
<th>Usual Care group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude estimate</td>
<td>0.47 (0.32 to 0.69)</td>
<td>0.76 (0.52 to 1.12)</td>
</tr>
</tbody>
</table>

Risk ratio for having diffuse pain at 3 months in the usual care group vs. MEDIC group

<table>
<thead>
<tr>
<th>Crude estimate</th>
<th>MEDIC group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude estimate</td>
<td>0.91 (0.52 to 1.60)</td>
</tr>
</tbody>
</table>

1 The definition of diffuse knee pain is from the Knee Pain Map32,33.
Table 5. Usage of pain medication

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MEDIC group (95% CI)</th>
<th>Usual Care group (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of users of pain medication¹ (n_MEDIC, n_usual care)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (42, 44)</td>
<td>0.69 (0.53 to 0.81)</td>
<td>0.55 (0.40 to 0.69)</td>
</tr>
<tr>
<td>3 months (42, 44)</td>
<td>0.45 (0.31 to 0.61)</td>
<td>0.66 (0.51 to 0.78)</td>
</tr>
</tbody>
</table>

Risk ratio for taking pain medication at 3 months vs. baseline

| Crude estimate                      | 0.66 (0.47 to 0.92)  | 1.21 (0.92 to 1.58)       |

Risk ratio for taking pain medication at 3 months in the usual care group vs. MEDIC group

| Crude estimate                      | 1.46 (0.98 to 2.17)  | -------------------- |

¹ User of pain medication was defined as patients taking pain medication of any kind on a regular basis during the last week.