Painful Knee Osteoarthritis demonstrates features of sensitization that correlate with synovitis detected by magnetic resonance imaging

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Background: Osteoarthritis (OA) is the most common arthritis worldwide and the most debilitating factor in OA is pain. Pain in OA is likely to be multifactorial, with features of nociceptive and mechanical pain. Recent work has suggested that pain 'sensitization' is also a feature of OA pain. 'Sensitization' is described as the phenomenon of heightened pain perception, mediated by increased firing of peripheral nociceptors, which may be experienced by a person at a local site related to damage or injury, also known as peripheral sensitization. When a person experiences heightened sensitivity even at distal sites from the local injury or damage, it is often described as central sensitization. Current measures of OA pain assessment in the clinic do not ask any questions about sensitization. We aimed to establish if phenotyping pain using clinical measures including painDETECT and quantitative sensory testing with pain pressure thresholds (PPT) can help establish more specific pain phenotypes in knee OA. In addition, studies have demonstrated that ongoing active synovitis detected by imaging is associated with high symptom burden in OA. Recent work has suggested certain components of OA pain are related to synovitis e.g. pain sensitization.

Methods: We recruited 62 participants with knee OA from a tertiary orthopaedic centre who were undergoing total knee replacement (TKR) for OA. Our study was conducted with full ethical approval (UKCRNID 15707). All participants underwent magnetic resonance imaging (MRI) within 6 weeks before their joint replacement using a 3T Philips MRI scanner. Participants were also asked to complete detailed questionnaires about their pain characteristics using the painDETECT questionnaire and underwent quantitative sensory testing using a Somedic hand-held algometer. Baseline pain scoring was carried out using the 0-100 mm visual analogue scale (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The level of joint damage was measured using the MRI Knee Osteoarthritis Score (MOAKS) and was assessed for synovitis score, bone marrow lesions and cartilage damage by 2 radiologists independently and a consensus score reached.

Results: We found that the mean visual analogue score (VAS) for pain of participants pre-knee replacement was 5.92 and 2.24 post-replacement. The median WOMAC score pre-knee replacement was 1424 and post-replacement was 845 ($p<0.0001$). We also assessed other features of pain using the painDETECT questionnaire for assessing pain sensitivity. We found 'possible' or 'likely neuropathic' elements to pain in a high proportion of participants pre-operatively: 44%, but only down to 27% after TKR, suggesting that more than one quarter of subjects had features of pain sensitization even after TKR. There was a positive correlation between VAS pain and Pain Pressure Thresholds (PPT) in our study (R squared 0.09, $p = 0.02$). Pain sensitization measured by PPT in our study was positively correlated with painDETECT ($p<0.05$). We found that, similarly to painDETECT, the objective measures of pain using QST before joint replacement were high: all the subjects who demonstrated features of pain sensitization at the knee had reduced PPTs sites distal to their joint damage, detected at the radius. MRI results demonstrated an increase in synovitis score was associated with increase in WOMAC pain ($p<0.0001$). When we evaluated the nature of structural damage by knee MRI using the validated MRI knee osteoarthritis score (MOAKS) we found that all subjects had significant joint damage as evidenced by cartilage loss, BMLs and synovitis. Increases in synovitis/effusion score (1: Mild, 2: Moderate, 3: Severe) were associated with increased pain sensitization by PPT ($p<0.0001$, Wilcoxon signed Rank Test).

Conclusion: Our results demonstrate that there are distinct phenotypes of pain in OA, some of which improve after treatment with TKR, but others who continue to demonstrate features of pain 'sensitization' in OA. The strongest structural correlate of pain sensitization in our study was increasing synovitis/effusion scores that were associated with reduced pain thresholds.

Study number = 62	Parameter
Age **Mean, SD**	**Range: 51-88** **68.7 +/-7.82**
Gender	**83.9 % female, 16.1 % male**
VAS pre-TKR **Mean, SD**	**5.92 +/- 3.84**
VAS post-TKR **Mean, SD**	**2.24 +/- 2.12**
PainDETECT pre-TKR **With likely neuropathic features**	**44%**
PainDETECT post-TKR **With likely neuropathic features**	**27%**