## Pain sensitisation in osteoarthritis

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#### ABSTRACT

Treating chronic musculoskeletal pain, and chronic joint pain (osteoarthritis (OA)) in particular, is challenging as the peripheral and central pain mechanisms are not fully discovered, and safe and as efficient analgesic drugs are not available. In general, the preclinical models of OA are limited to provide fundamental understanding of the pain mechanisms involved in patients with chronic joint pain (1). The pain associated with joint discomfort is highly variable, often underestimated by clinicians, and shows only modest association with crude radiological scorings. One reason for the disconnect between the extent of structural damage and pain is neuroplastic changes occurring in the peripheral and central nervous system resulting in pain sensitisation impacting the patient's experience of pain.

In recent years, a variety of human quantitative and mechanistic pain assessment tools (Quantitative Sensory Testing, QST) have been developed, providing new opportunities for diagnostic phenotyping of OA patients and the associated degree of sensitisation. Mechanistic phenotyping has revealed specific subgroups of specifically sensitised OA patients, and been used as a predictive guideline to evaluate which patients are most likely to experience continued chronic pain after an otherwise technically successful knee replacement (chronic postoperative pain). Furthermore, such techniques may be used to profile new or existing drugs together with other e.g. cognitive or behavioural therapies with the potential to manage joint pain.

#### Introduction

The management of chronic joint pain (osteoarthritis (OA)) has not been developed significantly for many years, compared with other joint related diseases (*e.g.*, rheumatoid arthritis - RA). One reason for this has been the much more exciting mechanisms of inflammation in RA leading to greater understanding of pathogenetic development of new biologic agents. Pathogenetic mechanisms in OA are less understood; however, much more prevalent than RA and is expected to increase significantly in the future due to ageing of the population.

A general consensus is that the animal models of OA and rheumatoid arthritis are limited in application to the clinic, reflected by the fact that many drugs active in animal models have failed in clinical joint pain trials (2-4). However, animal studies have consistenly shown that nociceptive activity from joints is particularly potent in central consequences such as segmental and extrasegmental sensitisation (5). The release of neuropeptides from activated joint nociceptors may initially lead to peripheral sensitisation. In damaged or inflamed joints, the continuous nociceptive input is the main driver of the central consequences leading to generalised sensitisation (6).

Neurophysiological animal experiments have shown that dorsal-horn-wide dynamic range neurons exhibit prolonged neuronal discharges, increased responses to non-noxious and noxious stimuli, from the joint and expansion of the receptive field (7). Likewise, it is known that an intact neuroaxis is important for maintaining healthy bones and hence joints (8). The impaired function of the sensory joint innervation as a function of age has been shown to accelerate degenerative cartilage degradation, facilitating development of OA (9). The joint structure is innervated by mechanosensitive, nociceptive and sympathetic nerve fibres located in the different structures such as subchondral bone, periosteum, periarticular ligaments, fibrous capsule, adipose tissue, meniscus, perimeniscal tissues, periosteum, periarticular muscle, and synovial layers, the articular cartilage is under normal condition avascular and aneural (10). A variety of animal OA models (spontaneous, surgically provoked, chemically induced) have been developed (3). The animal OA models are often developed in young male animals, although clinical OA is normally a manifestation of age with a higher prevalence in females. Although rodents also develop spontaneous OA with age, it is difficult to use this approach as an experimental model, as temporal development is unpredictable. In humans, overweight and obesity are known predictors of the development of OA, and this is also seen in animals, but again this model is difficult to implement as many other factors may contribute to the development (11).

In brief, animal models have taught us the importance of the neuroplastic changes in joint pathologies, for the facilitation of pain transduction and central pain processing, which conceptually has been important for understanding why many patients complain of more pain than the structural changes can account for. This phenomenon contributes to underestimation of pain by health professionals in many patients with musculoskeletal disorders (12).

Continuous and intense nociceptive input from a joint in animals may drive central sensitisation (6). This process has also been identified as an important mechanism in human OA (13, 14). Based on recent reviews on quantitative sensory testing (15, 16), it is concluded that peripheral and central sensitisation are prominent phenomena in OA.

A high degree of general sensitisation in OA has been shown to be related to high levels of pain (14, 17), disability, poor quality of life (13), increased spreading sensitisation (18), poor outcome after total joint replacement surgery (19, 20), and high concentration of pro-inflammatory cytokines (21). It appears of importance to have tools available to quantify the degree of sensitisation in OA and possibly use these tools in pain management to prevent further development of the pain chronification process (22).

For the individual OA patient, there often is a relative weak or almost no association between the actual tissue damage and the associated pain intensity (23-25), somewhat less apparent on a population basis (26, 27). Further-

more, 30–50% of patients with severe OA joint damage are asymptomatic, whereas approximately 10% with moderate to severe knee pain have normal x-rays (24, 28). Furthermore, a 10% to 20% of individuals with a regional pain problem subsequently develop widespread pain (29-31), particularly seen in joint pain conditions. The extent of bone marrow lesions appears linked to the OA pain intensity (32-34).

In general, OA patients are more sensitive to various experimental painful stimuli compared with age-matched controls (21), as 70% of knee OA patients are having at least one somatosensory abnormality (35). Both widespread (36) and local allodynia (37, 38) as signs of sensitisation have been documented in OA compared with control subjects. The role of pain sensitisation in OA has now been recognised and is being implemented as an assessment method in the clinic for diagnostic phenotyping. As a result, particular groups of OA patients have now been identified; e.g., patients with a low Kellgren & Lawrence score (KL2) and with very intense pain have been shown to suffer from severe sensitisation (17, 39, 40). Such a group of patients should most likely not undergo surgery as the outcome may be compromised, nonetheless, attempts should be made to manage the pain with drugs, normally used for treating neuropathic pain (e.g., anticonvulsants or antidepressants).

The development of human mechanism-based experimental pain biomarkers provides a new potential strategy to investigate aspects of the sensitisation mechanisms involved in joint pain. For diagnostic purposes, the experimental techniques may be used to quantify the increase (gain of function) or decrease (loss of function) in sensitivity of the nociceptive system and to evaluate the status of specific pain mechanisms. The aims of this paper are to discuss i) the mechanisms involved in joint pain, ii) how such mechanisms may be assessed quantitatively for diagnostic purposes in joint pain patients, and iii) the implications of diagnostic phenotyping for the management strategies.

More detailed information is presented in a recent review (41).

#### Assessing sensitisation in OA

Fundamentally, two applicable procedures are available to assess pain and pain sensitisation in OA: Clinical assessments using scores/questionnaires or experimental assessments using quantitative mechanistic pain biomarkers.

For clinical assessments, attempts have been made to develop questionnaires designed to depict sensitisation in OA, although "no gold standard" for assessment has been established. The standard techniques used are visual analogue scale (VAS) and other rating scales such as McGill Pain Questionnaire (MPQ) and its short form (SF-MPO). Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Health Assessment Questionnaire (HAQ), Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and Disease Activity Score (DAS28) (42). More recently the painDETECT Questionnaire has been developed to help classify joint pain patients into a nociceptive group and a neuropathic group (43). Although studies have identified neuropathic pain descriptors in joint pain patients (44-46), a comparison between the painDETECT and the Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) showed low agreement (47). As there is no gold standard for assessing centralised sensitisation, attempts have been made to develop more questionnaires (48); however, so far they have not shown to be particularly informative and useful in quantifying centralised sensitisation.

The characteristics of joint pain are different from, e.g., cutaneous pain which is normally superficial and localised around the injury with a burning and sharp quality. Pain localisation is generally poor from a joint and the surrounding structures, and therefore it is difficult to associate the pain to tendons, ligaments, bones or to the joint and its capsules. In OA, the number of painful joints is important for how diffuse the OA knee pain is perceived (49), most likely as a proxy for the degree of centralised sensitisation, supporting the notion that central sensitisation may be present in these patients (50). Therefore, mapping the area of OA pain is

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a simple method to follow progression and the spatial characteristics (from localised to diffuse).

In recent years, human quantitative pain biomarkers or quantitative sensory testing (QST) has been developed to provide test platforms to assess specific pain mechanisms and sensitisation in OA (15). Such psychophysical tests may be divided into stimulus-dependent and response-dependent methods. The stimulus-dependent methods are based on adjustment of the stimulus intensity until the pain detection or tolerance threshold is reached. The responsedependent methods rely on pain intensity ratings to a series of fixed stimulus intensities, and a score to each stimulus (e.g., VAS). The stimulus intensity normally varies in the interval between pain detection and pain tolerance.

Predominantly, four stimulus modalities have proven to be useful for assessing the consequences of OA on pain sensitivity: a) Pressure pain thresholds, b) thermal thresholds, c) cold pressor evoked pain, and d) pin-prick. In knee OA, the sites tested are normally around the knee (patella, medial and lateral aspects of the knee), muscles around the knee (quadriceps and tibialis anterior) and sites away from the knee (forearm, finger and trapezium) for assessing both the localised and the generalised pain hypersensitivity (Fig. 1).

A few studies have examined the reliability of experimental pain assessment in OA (51, 52) and found good reliability between experimenters and between sessions.

When comparing males and females with symptomatic knee OA, females tend to have lower heat, cold, pressure thresholds/tolerances, greater temporal summation of pain, as compared with males (53). The techniques most often used to quantify the degree of sensitisation in OA patients are application of a localised pressure stimulus or application of a tourniquet cuff around the arm/ leg (13, 14, 21, 35, 54-58). Although the experimental test stimulus provokes a different pain experience compared to clinical joint pain, it offers translational information on pain mechanisms with the potential to enhance the management of the disease (54, 54).

In general, OA patients are more sensitive to various painful stimuli compared with age-matched controls (21), with 70% of knee OA patients having at least one somatosensory abnormality (35).

A significant correlation between pressure pain sensitivity and symptom severity has been reported (55, 59). However, Skou *et al.* (60) found no association between pressure pain and clinical pain intensity. In general, the pain hypersensitivity is mostly pronounced in OA patients with the highest clinical pain ratings (61) and the longest pain duration (40).

Several recent meta-analyses (15, 62) and reviews (16, 63) have been published providing comprehensive analyses of all relevant sensory tests investigated in OA.

#### Mechanistic assessment of localised and generalised pain sensitisation mechanisms in OA

Recent human OA studies have showed promising translational features related to peripheral and central sensitisation (64).

OA progression generally is associated with loss of function and the fact that the patients have had pain of a certain intensity for a long time will drive the progression of sensitisation. Three specific mechanisms translate well from preclinical OA studies: 1) local *versus* wide-spread hyperalgesia; 2) temporal summation, and 3) descending pain modulation.

Local versus wide-spread hyperalgesia Pressure pain thresholds using a pressure algometer can be used to assess the pain sensitivity from the knee area (Fig. 1) versus an extrasegmental (Fig. 2) site, and thereby provide information about the extrasegmental spreading of sensitisation. Spreading sensitisation is consistently found to be a feature in OA (13, 14, 21, 35, 55, 57, 58), and depends on the clinical pain intensity and pain duration (63).

#### Temporal summation

Animal studies have shown that repeated nociceptive bombardment of dorsal horn neurons will render the neurons in a more excitable stage (called windup). The importance of the central integration of repeated nociceptive input is prominent in pain conditions with peripheral nociceptive drivers such as OA (called temporal summation).

Temporal summation is a measure for central integrative mechanisms induced by a sequence of stimuli with the same intensity; if the central pain system is in a hyperexcitable stage, the temporal summation will be strongly facilitated. Thereby the temporal summation is a proxy for central hyperexcitability.

It has been shown that facilitation of temporal integration develops in cats with naturally-occurring OA, providing an opportunity to use such a biomarker in translational research with the focus on joint pain (65).

Temporal summation can be elicited in OA patients by applying, *e.g.*, 10 identical stimuli with 1 sec interval where the  $10^{\text{th}}$  stimulus is perceived more painful compared with the  $1^{\text{st}}$  stimulus. In sensitised OA patients, this difference in pain intensity is much greater than in controls (63). Temporal summation can be evoked by a variety of stimuli such as tactile pin-prick, pressure, heat, and electrical pulses.

For simple bedside testing temporal summation evoked by repeated mechanical punctate pain stimuli has been used in OA (17, 61, 66) and the summation has shown association with the patient self-reported pain severity but not the radiographic severity (59). The subgroup of OA patients with "low KL and high pain" showed more facilitated temporal summation to punctate pain stimuli than other groups (17).

The most recent and reliable technologies developed for assessing temporal summation in OA have been repeated pressure stimuli using computer-controlled pressure algometry or cuff algometry. Both have shown facilitated temporal summation in OA with an association to patient-reported pain severity and duration but not radiographic severity (14, 40, 60).

#### Descending pain modulation

In animals, wide dynamic range (WDR) neurons (convergent neurons) are inhibited by nociceptive stimuli applied to a segment remote from the



**Fig. 1.** By assessing the pressure pain thresholds from many different locations over the knee joint it is possible to calculate a pressure pain sensitive map. The individual thresholds are colour-coded (RED = low pressure pain threshold = high pain sensitivity; BLUE = high pressure pain threshold = low pain sensitivity) and a topographical map can be constructed and overlaid a MRI-based contour image. Local tender spots (localised sensitisation) can be identified and the relative changes in pressure pain sensitivity can easily be visualised. In case of localised sensitisation in combination with centralised sensitisation the entire knee is being more sensitive but still the spots with localised sensitisation will be visible. This technique is useful for phenotyping knee OA patients.



**Fig. 2.** A schematic figure of local (localized sensitisation) and extrasegmental (centralised sensitisation) pressure pain thresholds assessed from the OA affected knee and the arm, respectively. In OA patients localised and centralised sensitisation will manifest with lower pressure pain thresholds from the affected knee (light orange bars) and the arm (light orange bars) as compared with the controls (green bar). In case a total joint replacement (Post Total Knee Replacement (Post-TKA)) with no chronic postoperative pain after TKA the thresholds normalises (green bar). In case of chronic pain after TKA even more localised and centralised sensitisation develop (lower thresholds, dark orange bars) as compared to the stage before surgery. For patients undergoing revision surgery (revision TKA) and continue to have chronic postoperative pain will show even more pronounced localised and centralised sensitisation (red bars).

excitatory receptive fields (67). Animal studies have shown that both descending facilitation and inhibition have an impact on the entire neuroaxis, explaining generalised widespread hyperalgesia, and may likewise have an important role in maintaining central sensitisation (68-70).

This pain inhibitory phenomenon is called "diffuse noxious inhibitory con-

trol (DNIC)", and DNIC-like effects triggered in humans are termed "Conditioned Pain Modulation (CPM)" (71). CPM can be assessed as pain inhibition of a given painful test stimulus when applied together with a tonic painful stimulus (the conditioning stimulus) (pain-inhibits-pain phenomenon).

As this mechanism is important and assessment technologies are available, the consequence has been an increased focus on the descending pain pathways in patients with chronic pain, particularly in OA patients. However, in humans we can only assess the balance (net sum) between the inhibitory and facilitatory pathways, and the general finding is that in chronic pain patients the potency of the pain inhibition is impaired (72, 73). This is particularly evident in patients with musculoskeletal disorders in general (74) and OA in particular (40). The neurotransmitters involved in descending modulation are, e.g., serotonin and norepinephrine, and agents which boost these neurotransmitters will further reduce pain (75, 75). A drug like duloxetine is shown to reduces knee OA pain (76, 77)

Preoperative CPM can predict the risk of developing postoperative chronic pain in patients undergoing thoracotomy (78), and is shown to be a reliable bedside measurement in women with chronic pain (79).

Studies in patients with painful OA have shown that impairment of descending pain inhibition is associated with both stronger pain intensity and pain duration (14, 40, 57, 80). Further, it has been found that the CPM is restored in patients after knee replacement when the patients become painfree (55). OA patients with chronic pain after knee replacement continue to have impaired descending control (60). However, Finan *et al.* (17) found no difference in CPM potency between different sub-groups of OA patients.

Studies have challenged the reliability of CPM assessments due to the large inter- and intra-individual variation (81) and various attempts have been made to refine the technique (82). Recently the cuff algometry technique has been applied, with one cuff delivering the conditioning stimulus and another cuff delivering the test stimulus. This method has shown consistent results across various OA studies (83, 84).

# Pre- *versus* post-operative sensitisation

Total joint arthroplasty (TJA) surgery is considered to be effective for end-stage knee osteoarthritis (OA) to improve function and reduce pain. By 2030 the incidence of total hip arthroplasty (THA) and total knee arthroplasty (TKA) in the US is believed to increase by approximately 200% and 700%, respectively (85). Prosthesis-related outcomes such as radiographic appearance of the prosthesis, implant survival, or surgeon-assessed outcomes are highly successful after TJA. However, while most patients experience pain relief after TJA, approximately 20% of TKA and 10% THA patients continue to have chronic pain post-operatively (86, 87). Understanding pain is complex and a single pre-operative measure cannot predict chronic post-operative pain. However, several pre-operative factors such as socio-economic factors, pre-operative pain intensity, pain sensitisation, arthritis in multiple joints, co-morbidities, pain catastrophising, genetic factors, inflammation, and previous surgery, are linked to the development of chronic post-operative pain following TJA.

Using experimental mechanistic pain biomarkers, pre-operative widespread hyperalgesia is found to be linked to the development of chronic post-operative pain following TJA (20, 83) (Fig. 2).

Pre-operative temporal summation has been shown to predict the development of chronic post-operative pain following total knee replacement surgery (83, 88) and is facilitated more in patients with pain after total knee replacement compared with those who become pain-free (89). In those with no chronic post-operative pain after joint replacement, temporal summation will be normalised (55). In addition, those patients with chronic pain after knee replacement showed even more facilitated summation as compared with OA patients prior to surgery both at the individual level and as average for the group as compared with those who are pain free after surgery (18).

Impaired descending pain control in OA patients before surgery is restored after successful knee replacement in those patients where the pain has been resolved (55).

Pre-operative impaired CPM in combination with facilitated TSP has been found to be predictive of development of chronic post-operative pain after TKA (88) suggesting that the combination of different experimental pain biomarkers together with the clinical predictive features may be a useful approach for further development of a "predictive pain platform".

Up to 50% of OA patients will experience pain after revision joint surgery (87) and show further enhanced widespread hyperalgesia, facilitated temporal summation and lower CPM compared with patients with no pain after revision joint surgery (60) and they will have even more pain (18, 60) as compared to both before and after the primary operation. Revision surgery based purely on the indication of pain should be thoroughly re-considered.

#### Conclusion

The fundamentals of OA progression and the neurophysiological correlates are not fully explored and understood. In recent years, the roles of the nervous system in development and manifestations of OA have become progressively more evident. The neuroplastic changes occur as the disease progress eventually results in sensitisation, which leaves patients with more pain than might be expected based on actual structural joint damage. Experimental pain biomarkers have been developed to assess different sensitisation mechanisms involved in painful OA offering the opportunity to phenotype patients and identify specifically highly sensitive groups. Future perspectives are to match the sensitisation phenotype with type of pharmacological interventions and work towards personalised pain management regimes.

Likewise, the recent developments have provided new opportunities to provide predictive sensitisation indications for patients most likely to develop chronic postoperative pain after a joint replacement. It is now evident that repeated surgeries solely on the indication of pain most likely will render many patients in more pain and with more sensitisation.

Better understanding and clarification of the central mechanisms involved in chronic joint pain may help developing new and better analgesics for OA pain.

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