
Identifying pain susceptibility phenotypes in knee osteoarthritis

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ABSTRACT

Knee pain in osteoarthritis is complex and complicated by the fact that osteoarthritis is considered to be a disorder of multiple phenotypes. This complexity challenges our understanding as to why some people remain relatively symptom-free, while others progress to persistent pain. One approach to understanding the mechanisms underlying the transition to persistent pain is by identifying pain susceptibility phenotypes in people with or at risk of knee osteoarthritis. Using variables representative of the multidimensional nature of pain in people who were free of persistent pain, we identified four phenotypes characterised by low pressure pain thresholds and temporal summation and not psychosocial factors in those who developed persistent pain two years later. The group with the highest proportion of low pressure pain thresholds and a moderate proportion with facilitated temporal summation had twice the odds of developing persistent knee pain. This work provides preliminary insights into the critical importance of altered neurobiological mechanisms of pain signalling that contributes to development of chronic, persistent pain in knee osteoarthritis.

Knee pain in osteoarthritis (OA) is complex and somewhat paradoxical due to the often reported structure-symptom discordance (1). Patients with a low degree of radiological OA, but high self-reported pain intensities have been found to be a specific subgroup of OA patients who are very pain sensitive (2). Add to this the fact that OA is considered to be a disorder of multiple phenotypes or pathophysiologic pathways, rather than one defined by a single process, and the level of complexity increases further (3). In two systematic reviews of phenotypes in OA, ‘chronic pain with prominent features of central sensitisation’ and ‘pain sensitisation’ have been identified (4, 5). Substantial

evidence suggests that in people with knee OA, widespread pressure hyperalgesia, facilitated temporal summation (TS) of pain and impaired conditioned pain modulation (CPM) are commonly reported compared with healthy individuals (6-8). Taken together, this indicates sensitisation of central pathways carrying both facilitatory and inhibitory signals influences the experience of pain and interpretation of its causes. Patients who exhibit alterations in neurophysiologic nociceptive signal processing seem to respond poorly to standard OA treatments (7). Despite recognition of the presence of sensitisation in people with knee OA, there continues to be a lack of understanding as to why some people remain relatively symptom free, experiencing only intermittent, often activity-related, pain while others progress to persistent pain.

To examine the complexity of pain and its progression to a more chronic state, we must ensure that the multidimensional nature of pain and its biopsychosocial components are adequately considered. One potential way to achieve this and to account for heterogeneity in the disease process observed in people with knee OA is through the use of phenotyping. A phenotype is defined as the composite of an organism’s observable characteristics or traits, including morphology or physical form and structure; its developmental processes; its biochemical and physiological properties; its behaviour, and the products of behaviour (9). This definition has been adapted to be more specific for the context of pain with the addition that it includes patient self-reported characteristics (*e.g.* psychosocial functioning), patient-reported symptoms (*e.g.* sleep disruption), and verbal or behavioural responses to standardised psychophysical tests of pain sensitisation (10). The interest in determining OA phenotypes and optimising methods used to do so, has increased in recent years as a means to improve treatment targets and

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provide a more personalised approach to medicine (11). Specific to pain and chronicity, the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials has recommended specific variables and measures for pain phenotyping based on current best evidence (10). Some earlier work in examining symptom-related phenotypes in OA aimed to understand the predominant contributions to the pain experience in individuals with OA. For example, in a sample of older adults with symptomatic knee and hip OA, three groups of individuals were identified. One group had symptoms reminiscent of fibromyalgia, with high pain, fatigue, depressive symptoms, poor sleep, and high somatic symptoms; a second group whose measures appeared to reflect mild depressive symptoms; and a third group with minimal symptoms except for sleep difficulties (12). A challenge with interpreting such studies is that it is unclear as to whether some of those features, such as sleep difficulties or depressive symptoms are a cause or consequence of the pain experience in OA. Nonetheless, identifying these additional features that contribute to pain has highlighted the need to evaluate other potential pain contributors or modifiers when managing people with symptomatic OA. Thus pain phenotyping in a group of individuals with existing symptomatic OA can help identify factors that clinicians should address in managing pain.

While there has been an advancement in understanding OA as a composite of different phenotypes, of which chronic pain and sensitisation have been identified as one phenotype, these studies to date have not provided insights regarding what causes individuals to *develop* chronic persistent pain in OA, the major reason for functional limitations, disability and diminished quality of life in OA (1). That is, studies to date have not provided insights into why some people transition from acute or intermittent pain to chronic, persistent pain while others do not during the course of their knee OA. We therefore sought to identify a phenotype of pain *susceptibility* and its characteristics (8). Doing so would provide the first step in

understanding mechanisms underlying the transition from acute, intermittent pain to chronic persistent pain and the eventual study of the prevention of this transition.

We used data from the Multicenter Osteoarthritis (MOST) study, an NIH longitudinal community-based study of people with or at risk of knee OA, which has the largest experience to date with sensitisation in knee OA, and the only cohort to date to have collected longitudinal data on pain sensitisation (8, 13). We were interested in understanding what factors may predispose individuals to developing chronic persistent pain beyond structural pathology itself. Using the variables available in the MOST dataset, our variables of interest to create the phenotype were those with a well-known association with the pain experience and adhered to the proposed definition for pain phenotyping (10). This included self-report measures of psychosocial function (pain catastrophisation and depressive symptoms), self-reported symptoms (presence of widespread pain and sleep quality) and responses to standardised psychophysical tests of pain sensitisation (pressure pain thresholds and temporal summation (TS)) at multiple sites (local - patella and tibia; remote - forearm). In addition to creating the phenotypes, we wanted to be able to characterise individuals in the respective subgroups to be aware of risk factors for phenotypic membership. Lastly our outcome of interest was the reporting of incident persistent knee pain two years later, defined as people reporting pain on most days of the month over two consecutive one-month periods. To identify new development of persistent knee pain, our sample consisted of people who were free of persistent pain at baseline, meaning that they were free of pain on most days during the baseline period of assessment over 2 consecutive one-month periods (8).

There were 852 subjects (55% female, mean age 67 years, mean BMI 29.5 kg/m²) who were free of persistent knee pain. Using an agnostic (unsupervised) latent class modeling approach to determine the number of phenotypes, a 4 class model was chosen based on fit sta-

tistics and current evidence based clinical knowledge. We labelled the classes according to the dominant features of the composition of the indicator variables and their proportions resulting in the following groups: 1. low-to-moderate proportion of people with both pressure pain sensitivity (~16–26%) and facilitated TS (33–35%) n=285; 2. low proportion-to-none with pressure pain sensitivity (0–6%) and facilitated TS (2–10%) n=265; 3. high proportion with pressure pain sensitivity (75–89%) and a moderate proportion with facilitated TS (53–58%) n=199; 4. high proportion with facilitated TS (82–90%) but a very low proportion-to-none with pressure pain sensitivity (0–4%) n=103. See Figure 1. Interestingly, none of the other non-QST variables (pain catastrophising, depressive symptoms, widespread pain and sleep quality) significantly informed the phenotypes. Assessment of the relationship of the phenotypes to development of persistent knee pain two years later, revealed that those in group 3 (high proportion with pressure pain sensitivity and a moderate proportion with facilitated TS) had twice the odds [OR 1.98 95% CI (1.07–3.68)] of developing persistent knee pain compared with those in group two (low proportion to none with pressure pain sensitivity and facilitated TS). Neither of the remaining groups had significant risk of experiencing incident persistent knee pain compared with group 2 (the group determined with the lowest degree of pain susceptibility). Examination of the various risk factors for membership in group 3, deemed to have the greatest degree of pain susceptibility, compared with group 2, revealed that females [OR 4.08 (2.68–6.22)], non-Caucasians [OR 2.47 (1.36–4.49)] and those 65 years or older [OR 1.88 (1.24–2.85)] were more likely to be found in the group 3. Of note, presence of radiographic OA did not differ between the 4 groups. We further conducted sensitivity analyses to assess more parsimonious models, as well as variable contribution to the original model. These confirmed the dominant contribution of the QST measures, particularly the pressure pain thresholds and the lack of contribution of the remaining variables (8).

When we had embarked upon identifying pain susceptibility phenotypes, we had hypothesised that altered nociceptive signalling, as assessed by QST, would be prominent in a certain group of individuals, and that they would be at higher risk of developing persistent knee pain. This hypothesis was supported by these data. However, we also hypothesised that a different set of individuals would have depressive symptoms or other such factors that predispose them to developing persistent knee pain. We did not find a unique cluster of such individuals. Indeed, as outlined above, the non-QST measures did not meaningfully differ between groups. Thus, it does not appear that depressive symptoms, poor sleep quality, or pain catastrophising predispose to developing persistent pain, though they do play a role in the severity of pain experienced. In addition, and in keeping with the so-called structure-symptom discordance, there was no difference between groups with respect to presence of radiographic OA, highlighting the fact that structural pathology alone does not lead to pain persistence. These results also highlight that older adults, particularly female and non-Caucasian, may be particularly vulnerable to have the QST abnormalities that appear to predispose to developing persistent knee pain. Why this may be is not clear presently, but does identify a research agenda to understand changes in nociceptive signalling with aging and in different racial/ethnic groups, potentially related to genetics and/or sociocultural influences, including chronic stress.

The findings of QST abnormalities being associated with development of persistent knee pain parallels similar findings of QST abnormalities being associated with pain persistence post-knee replacement surgery (7, 14). These observations are also in keeping with the finding that radiographic severity and duration of OA are not associated with presence of QST abnormalities, though pain sensitisation is associated with greater pain severity (6). Taken together, these findings appear to support the notion that pain sensitisation may be more of a trait than state (6), particu-

- 1- Low to moderate proportion of PP sensitivity and facilitated TS n= 285 (34)
- 2- Low/absent proportion of both PP sensitivity + facilitated TS n=265 (31)
- 3- High proportion of PP sensitivity + moderate proportion of facilitated TS n=199 (23)
- 4- Low proportion of PP sensitivity + high proportion of facilitated TS n=103 (12)

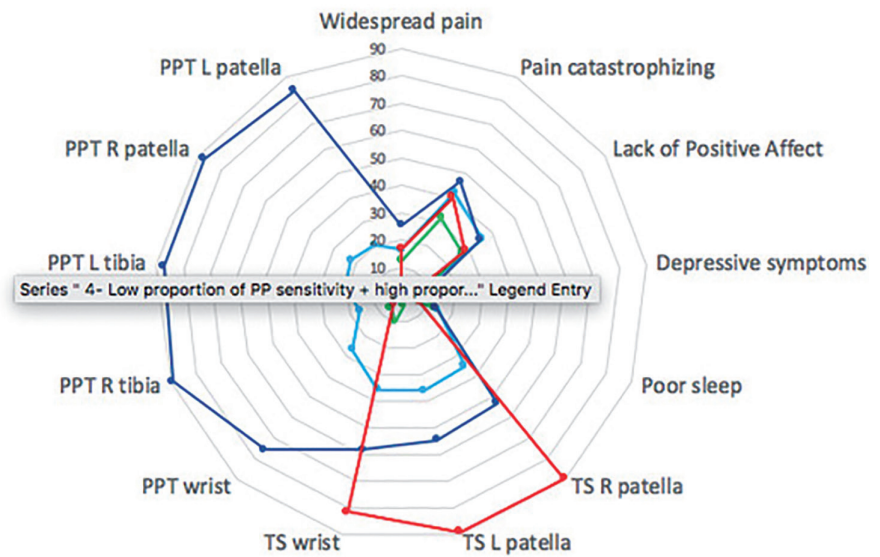


Fig. 1. Spidergram plot of identified classes, showing proportions of each indicator variable in each of the respective phenotypes. PP: pressure pain; TS: temporal summation; PPT: pressure pain threshold.

larly strengthened by the fact that QST abnormalities predated development of knee pain persistence in our cohort (8). What are the implications of altered excitability of peripheral nociceptors and the spinal cord, along with potential inadequate descending inhibitory modulation as contributors to development of pain persistence? Should we entertain a new concept of disease modification that refers to preventing establishment of persistent changes in the nervous system by early interventions? Some studies have begun testing these concepts in the setting of surgery, wherein preoperative treatment has been associated with better post-operative pain outcomes (15, 16). Further studies are needed, of course, but these initial studies provide some proof-of-concept to the idea of pre-emptive therapy. These studies raise the interesting question of whether treatment with drugs that may modulate pain sensitisation and/or conditioned pain modulation (*i.e.* descending inhibitory modulation) early in the course of OA may be reasonable to try to prevent the transition from intermittent to persis-

tent knee pain in those with knee OA in those who exhibit QST abnormalities. With development of easy-to-use QST measures or a validated questionnaire that is an adequate substitute, it may become feasible to implement pain phenotyping to facilitate testing whether mechanism-based approaches to pain management would result in better patient outcomes. Clearly, understanding the timing of the transition from intermittent to persistent pain and the role of sensitisation in this process is important to help inform when (if) pre-emptive therapy should be tested. A major unanswered question remains whether there is a point-of-no-return for some individuals wherein the changes in the nervous system may no longer be reversible. These questions, and others like these, inform yet a broader research agenda to better understand the course of altered neurobiological pain signalling over time. Just as there are radiographic stages of disease, there are likely different stages of pain in OA, reflecting alterations in neurobiological pain processing and potentially to what extent neuroplasticity remains.

Pain phenotyping, including pain *susceptibility* phenotyping, will be critical to understanding these concepts of stage of pain, and contributors to pain in a given individual.

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