Clinical perspective on pain and pain phenotypes in osteoarthritis

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Conflict of Interest

None

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Abstract

Purpose of review Pain is the most prominent symptom in osteoarthritis. Pain experience is a complex and multifactorial phenomenon. This review, therefore, offers a brief overview of the literature on factors from main pain dimensions and summarizes current evidence for identifying pain phenotypes in knee osteoarthritis.

Recent findings Peripheral structural damage has been traditionally considered a source of pain and this has strengthened with MRI studies; however, a discordance between structural damage and pain severity suggests individual variations in pain presentation which may be determined by genetic, environmental (obesity), psychological and neurological factors. Each of the factors may play its role or intact with other factors to contribute to the variation which can partly explain the overall lack of treatment efficacy with the current 'one-size-fits-all' treatment approach. Identifying pain phenotypes in knee osteoarthritis is promising to develop individualized treatments; however, the validity and reliability of osteoarthritis pain phenotypes have not been tested in clinical practice.

Summary Given the heterogeneity of osteoarthritis pain, peripheral, psychological and neurological factors are considered key phenotypic dimensions in the identification of pain phenotypes. This new concept allows for patients' stratification for clinical trials, thus providing the potential for individualized interventions in patients with osteoarthritis pain.

Keywords Knee Osteoarthritis, Pain, Phenotypes, Treatment

Introduction

Osteoarthritis (OA) is the most common form of joint disease worldwide affecting 9.6% of men and 18% of women aged more than 60 years [1]. It is a chronic and painful disease of the synovial joint and the most common cause of chronic disability [2]. Knees, hips and hands are the most commonly affected joints. Pain is the most prominent symptom of OA which drives patients to seek healthcare. Thus, OA represents an enormous health and economic burden on patients and societies.

There are no proven strategies to prevent, slow, halt or reverse the OA progression. Current OA management is mostly palliative and focuses on pain relief. There is no single ideal medication for management of pain. 'First-line' agents, such as paracetamol and non-steroid anti-inflammatory drugs (NSAIDs), have only small to moderate efficacy, with >75% of patients reporting the need for additional symptomatic treatment [3]. Therefore, pain control remains a substantial unmet need in OA treatment.

Furthermore, OA is a heterogeneous condition characterized by a complex and multifactorial nature [4]. This leads to a large variation in pain presentations and responses to OA treatment. Some studies have considered disease or structural progression to identify knee OA phenotypes with few reports on pain phenotypes [4]. The pain experience is a complex phenomenon affected by factors across multiple domains–peripheral, psychological, and neurological [5]. This complexity has hindered the identification of pain phenotypes in prior work. Peripheral structural damage in the knee has historically been thought to be the key origin of pain in knee OA; however, a weak association between radiographic structural damage and knee pain [6] raised the possibility of individual variations in pain presentation which may be mediated by genetic, environmental (obesity), psychological and neurological factors. The exact etiology and mechanisms of each factor contributing to OA pain are far less well known. This review, therefore, offers a brief review of the literature on these factors associated with OA pain and summarizes evidence for identifying pain phenotypes in knee OA.

Factors associated with OA pain

Genetic factors

Robust inter-individual differences in pain experience are often observed in the clinical setting, raising the possibility that the inter-individual variability in the experience of pain

may be due to differences in pain sensitivity which is probably affected by underlying genetic factors [7]. Earlier twin and epidemiological studies have demonstrated that pain sensitivity *per se* is heritable [8, 9], although it has been suggested that a range of factors such as prior experience, expectation, and current mood modulate the experience of pain and these factors themselves are genetically mediated [10-13]. The estimates of heritability from studies range from 9% to 60% for different pain traits [10, 11, 14]. The heritability of knee pain was estimated at 44% in a sib-pair study from our group [15].

Research has been trying to search for genes that might predispose individuals to the development of chronic pain or experiencing greater pain sensitivity. There were two categories (linkage and candidate-gene studies) that the majority of studies have fallen into. A variety of genes identified have been shown to be tentatively associated with pain states [16, 17]. As in other fields, there have been inconsistent associations in the replication across populations or across pain conditions. Other than the general reason for inconsistent results in genetic studies including sample size, pain definition, *etc*, the pain field struggles with the existence of complex pain phenotypes [16]. For example, pain conditions are quite heterogeneous even if one could identify genetic associations with specific pain conditions, such as low back pain, or there are a number of subcategories while investigating a broader category of clinical pain [7, 16]. Recent years have seen an explosion of genome-wide association study (GWAS) in the identification of risk alleles; however, GWAS in human pain has lagged behind than in other fields, for reasons such as difficulties in undertaking the quantitative phenotyping of this subjective phenomenon [18]. At present, there is only one adequately powered GWAS conducted for chronic widespread pain (CWP) [19].

Relative to numerous genomics studies in OA, only a few studies have examined genes that regulate OA-related pain so far. Currently, there are six genes identified with a possible association with pain in OA, as shown in **Table 1**. A common genetic variant of Val158Met in catechol-O-methyltransferase (COMT) gene which reduces the activity of the catecholamine degrading enzyme was identified to be associated with hip pain among those with hip OA [20]. Unfortunately, this SNP failed to be replicated for knee pain in an independent and adequately powered study [21]. Another gene SCN9A encoding the voltage-gated Sodium Channel 1.7 (Nav1.7) that is essential for transmission of pain-related signals, was initially shown to associate with greater pain in a study with 578 OA patients [22], and held up in a larger cohort of replication study [23]. Some other candidate genes have been examined and have confirmed associations with OA-related pain, including transient receptor

potential cation channel subfamily V member 1 (TRPV1), P2X7 and proprotein convertase subtilisin/kexin type 6 (PCSK6) [24-26]. More recently, one of six SNPs in the neurokinin 1 receptor (TACR1) has shown a nominally significant association with a decreased risk of symptomatic OA in discovery cohort and then replicated in four additional cohorts [27].

Table 1 Genomics studies in osteoarthritis-related pain

Studies	SNP	Gene	Protein	Function of protein	Sample size (n)	Ethnic group	Source
Initial study							
	rs4680	COMT	Catechol-O-methyltransferase	Degradation of catecholamine neurotransmitters such as norepinephrine and dopamine	288 (radiographic hip OA)	Caucasian	[20]
					171 (female radiographic hip OA)	Caucasian	
	rs6746030	SCN9A	Voltage-gated Sodium Channel 1.7 (Nav1.7)	Nociception signalling	578 (symptomatic OA)	Caucasian	[22]
	rs8065080	TRPV1	Transient receptor potential cation channel, subfamily V, member 1	Thermosensitive channel	7122 (3270 symptomatic knee OA and 3852 controls)	Caucasian	[24]
					4950 (1098 asymptomatic knee OA and 3852 controls)	Caucasian	
	rs7958311	P2X7	P2X purinoceptor 7	Ionotropic ATP-gated receptors, affecting pore formation in cell membranes	1329 (743 symptomatic OA and 586 controls)	Caucasian and African American	[25]
	rs900414	PCSK6	PACE4 (paired amino acid converting enzyme 4)	Activating aggrecanases	756 (600 symptomatic knee OA and 156 asymptomatic knee OA)	Caucasian	[26]
					2742 (2068 symptomatic knee OA and 674 asymptomatic knee OA)	Caucasian	
	rs11688000	TACR1	Neurokinin receptor 1	Dopamine modulation in central nervous system	1615 (1232 symptomatic OA and 383 asymptomatic knee OA)	Caucasian	[27]
					2450 (1566 symptomatic OA and 884 asymptomatic knee OA)	Caucasian	
Replication	rs4680	COMT	Catechol-O-methyltransferase	Degradation of catecholamine neurotransmitters such as norepinephrine and dopamine	9556 (3934 symptomatic knee OA and 5622 controls)	Caucasian	[21]
					6781 (1159 asymptomatic knee OA and 5622 controls)	Caucasian	
	rs6746030	SCN9A	Voltage-gated Sodium Channel 1.7 (Nav1.7)	Nociception signalling	1854 (1325 symptomatic OA or TKR and 529 asymptomatic OA)	Caucasian	[23]

OA osteoarthritis; TKR Total knee replacement.

Structural damage/inflammation

Pain in OA has been considered nociceptive pain, arising from peripheral local tissue damage [28]. Cartilage, the primary site of OA pathology, is aneural and avascular, so it cannot generate pain directly, raising the possibility that pain may come from other structures or chemicals released by cartilage [28]. By contrast, subchondral bone, adjacent periosteum, synovial membrane, periarticular ligaments and joint capsule are richly innervated with the nerve fibres transmitting peripheral input to spinal cord [29]. However, imaging studies have widely reported a discordance between radiographic severity of OA and pain severity [30]. A systemic review of the literature concluded that 15-76% of patients with knee pain had radiographic OA, and 15-81% of patients with radiographic OA had knee pain [31]. This discordance is often explained by the insensitivity of X-ray to discern underlying pathologies contributing to pain [32]. Some studies have examined the relationships between structures on MRI and knee pain and reported inconsistent results [32]. This is supported by a recent literature review describing only thirteen of twenty-one studies reporting statistically significant associations of MRI findings in OA and symptoms [33]. **Table 2** summarizes the associations between structures detected on MRI and knee pain. Overall, the levels of evidence between structural features and pain are limited or conflicting, except for bone marrow lesions (BMLs) and effusion-synovitis which appear to have moderate levels of evidence supporting their relation to OA-related pain [30]. The lack of strong evidence of the association between structures detected on MRI scans or radiographs suggests that peripheral damage is not only one contributor to pain [34].

Table 2 Associations between knee structural factors detected by MRI and osteoarthritis pain

Structures	Evidence				
	No	Conflicting	Limited	Moderate	Strong
Cartilage defects		+			
Meniscal pathology		+			
Bone marrow lesions				+	
Bone attrition		+			
Osteophytes			+		
Effusion-synovitis				+	
Ligament tear			+		
Tibial bone size	+				

Adapted from a systematic review by Yusuf et al. [35]

Obesity

Since the end of the last century, the relationship between obesity and chronic pain has attracted extensive investigation. There is a sizeable body of evidence to suggest that obesity and pain adversely impact each other, and obesity is predictive of worse functional and psychological status of chronic pain [36]. Based on a US study in one million people, individuals with overweight (body mass index (BMI), 25–29.9 kg/m^2) reported 20% higher rates of pain, 68% higher for those BMIs of 30–34 kg/m^2, 136% higher for those BMIs of 35–39 kg/m^2 and 254% higher for those BMIs of more than 40 kg/m^2 compared to normal weight group [37]. Evidence from longitudinal studies suggests that obesity (even in childhood) is an important risk factor for the development of chronic pain, indicating that obesity is more likely a cause rather than a consequence of pain [38-40].

It has long been assumed that potential mechanisms underlying the relationship between obesity and pain may be due to mechanical loading, especially for lower extremities. There is a linear increment of compressive loading across the joint as BMI increases. In knee OA, relative to those with overweight, people classified as class 1 or 2+ obesity have greater peak knee compressive forces [41]. Similarly, weight loss has been shown to be effective in reduction of knee joint forces [42]. Increased joint forces may result in an aberrant biomechanical environment; it is, therefore, not surprising to observe greater structural damage in the loading joint in obese individuals. The evidence of the role of inflammation involved in the link between obesity and pain is accumulating because adipose tissue has been recognized as an endocrine organ responsible for producing and releasing

proinflammatory cytokines and adipokines [43]. Recent studies have shown an increased level of cytokines and inflammatory markers, such as C-reactive protein (CRP), IL-6, tumor necrosis factor (TNF)-α and leptin in obese individuals [44, 45]. In addition, the release of inflammatory markers also can be triggered by the breakdown products from structures or tissues damages due to aberrant loading [46, 47]. Elevated levels of these biomarkers lead to enhancing pain severity and its change [48, 49], which in turn stimulate more inflammatory markers release [50]. Mounting evidence suggests that inflammation can lead to a lowering of excitation threshold and enhanced responses to suprathreshold stimuli of peripheral nociceptors (peripheral sensitization) and subsequently developing central nervous system sensitization with pain hypersensitivity and increased vulnerability to reporting more pain sites [30, 51].

Psychological factors

As in other pain conditions, psychological factors have been found to be crucial contributors to the OA pain experience [52]. Two critically important psychological factors—depression and catastrophizing have shown consistent associations with increased pain severity, reduced pain threshold, impaired physical function and poor response to treatment [52]. Psychological factors exert their effects on pain through multiple interactive pathways from behavioural, cognitive to neurophysiological (details can be found in the review [52]). Briefly, the mechanisms by which psychological factors contribute to pain may include dysfunction of pain processing in the central nervous system [53-55], genetic vulnerability [19] and cognitive influence [56]. In the context of OA, psychological health is implicated in the pain experience [57-59]. Furthermore, there is a growing body of evidence showing that patients with preoperative depression and pain catastrophizing are more likely to have higher pain scores after total knee replacement [60, 61]. However, causal effects are hard to be discerned due to bidirectional relationships between psychological factors and pain [62].

Neurological factors

Various studies have shown pain in OA is neuropathic, reflecting that potential mechanisms of neuropathic pain are a consequence of the interrelation of peripheral and central sensitization mechanisms [63-65]. Joint injury and/or inflammation lead to the release of mediators into the joint which sensitize primary afferent nerves with a reduction in threshold and an amplification of responsiveness to suprathreshold stimuli of peripheral nociceptors (peripheral sensitization) [66-68]. As such, exaggerated responses to noxious mechanical

stimuli (primary hyperalgesia) can be evoked, and normally innocuous joint movement can evoke a painful response (allodynia) [30]. Increased peripheral neuronal activity further confers the alteration in pain processing by the central nervous system (central sensitization) including more responsive to peripheral input, an expansion of receptive filed of dorsal horn neurons as well as brain activation, sensitization and modification [34, 69]. Studies using quantitative sensory testing (QST) analyses and functional MRI have confirmed central sensitization in OA [65, 69]. The presence of central sensitization in OA may be predictive of more severe, longer duration and larger area of pain which does not respond to conventional analgesics [64].

Searching for pain phenotypes in OA

There have been numerous attempts to identify OA phenotypes in order to better target this heterogeneous condition. In a systematic review including 24 studies to identify knee OA phenotypes, Dell'lsola *et al* [4] proposed that there are existing six phenotypes based on key variables extracted from prior studies: chronic pain (central sensitization mechanisms are prominent); inflammatory knee OA; metabolic syndrome; bone and cartilage metabolism; mechanical overload; minimal joint disease. More recently, Deveza *et al* [70] identified knee OA phenotypes and their clinical outcomes in a review with 34 observational studies. The author found that poor clinical outcomes were linked to pain sensitization, psychological distress, radiographic severity, BMI, muscle strength, inflammation and comorbidities. Poor structural outcomes were associated with gender, obesity and other metabolic abnormalities, inflammation and cartilage damage pattern. Although these distinct phenotypes clearly show the variability in OA mechanisms and may represent different subgroups to benefit from different treatments, it remains unclear about whether mechanisms of OA pathology and OA pain might differ and therefore they can be considered discrete entities separately [71]. From a clinical perspective, a phenotype based on OA pain traits would be more clinically meaningful than structural characteristics given the fact that there are no approved disease-modifying drugs available and that there is a great discordance between pain intensity and the extent of structural damage.

While there is no agreement on pain traits selected to identify pain phenotypes in OA, studies have identified pain phenotypes mostly based on a single pain dimension and cross-sectional study design [70]. Profiling psychological factors, pain sensitivity, comorbidities and obesity were the most common investigation in prior studies; however, there were few studies on structural factors and across multiple pain dimensions including the factors mentioned above.

To date, only one cross-sectional study by Kittelson *et al* [72] identified four pain phenotypes in knee OA across multiple pain dimensions, including higher levels of comorbidities; higher knee joint sensitivity; higher levels of psychological distress; and minimal joint disease and pain. Structural pathology in this study was assessed by radiograph, other MRI structural lesions associated with OA pain such as BMLs and effusion-synovitis were not profiled. This is of clinical relevance to early interventions as early MRI structural damage might be reversible. To shed light on this question, we recently identified pain phenotypes using a wide spectrum of factors including main pain dimensions (structural damage on MRI, BMI, comorbidities, psychological and neurological factors) [73]. Three distinct pain phenotypes were identified: Class 1 participants having a high prevalence of emotional problems and low prevalence of structural damage; participants in Class 2 had a high prevalence of structural damage and low prevalence of emotional problems, and Class 3 participant had a low prevalence of emotional problems and low prevalence of structural damage. Furthermore, we found that participants in Class 1 had greater pain severity and number of painful sites than those in Class 2 and 3 over 10.7 years. This may also suggest that the phenotypes reflect distinct clinical prognosis.

Challenges in the identification of OA pain phenotypes

There are some challenges in identifying OA or OA pain phenotypes due to their heterogeneity and lack of in-depth understanding of mechanisms by which etiological factors contribute to OA and pain, as such it seems hard to determine which factors most reflecting the disease pathophysiology should be profiled, and whether factors included may overlap with each other through other pathways. This raises an important question of whether phenotypes identified which really represent distinct patient subgroups whose clinical presentations, prognosis and response to treatments are different. There is no consensus regarding the core data or traits recommended for defining phenotypes in the OA field. Despite the important role of genetic factors in pain pathogenesis, focusing on modifiable factors in clinical practice could allow for potential intervention. In our opinion, therefore, core data from knee structural, psychological and neurological domains are essential in the identification of OA pain phenotypes. However, advanced imaging techniques (e.g. MRI) and QST are not routinely utilized in clinical research and practice due to the cost and practicality. This may hinder to define a multidimensional phenotype and limit the potential use of the phenotype to inform stratified care in the clinical setting. Cross-sectional study design in prior studies aimed at identifying OA pain phenotypes was unable to validate the

stability of the phenotypes and determine whether phenotypes are relevant to clinical outcomes including prognosis and treatment response.

Individualized pain treatment based on phenotypes: are we there yet?

Currently, therapeutic interventions for OA are palliative and primarily focus on alleviating pain [74]; however, treatment for the management of OA pain is problematic and mainly targets the peripheral joint and peripheral nervous system. NSAIDs have been a mainstay treatment for OA pain, but the efficacy of these has been proven to be only moderate [75]. Intra-articular glucocorticoid injections and joint replacement surgery also play a key part in the management of OA, both targeting the peripheral mechanism of pain [76, 77]. Failure to relieve OA pain through these treatments is frequently seen in the clinical settings; for instance, there are approximately 7-23% and 10-34% of patients having long-term pain after hip and knee replacement surgery [78, 79], suggesting that treatments targeting peripheral mechanisms are insufficient for those patients.

Weight loss has been a focus in the treatment and management of OA pain. It has been demonstrated that weight loss in obese patients can reduce the risk of the development of symptomatic OA [80] and improve symptoms in OA patients [81]. There is a dose-response relationship between weight loss and pain improvement in people with symptomatic knee OA [82]. A combination of exercise and diet is recommended to achieve weight loss and a greater pain reduction [83].

With the appreciation of increasing understanding of psychological and neurological factors in OA pain, interventions targeting pain catastrophizing, cognitive behavioural therapy and pain coping skills training have drawn great attention, although the results were mixed. Other pain management strategies are emerging including sleep interventions and pain education [84-86]. The treatments (e.g. antidepressants) designed to target the central nervous system have shown effects on pain improvement in patients with knee OA [87, 88]; however, central sensitization does not exist in all patients with OA pain. It is likely that subgroup with this feature may have a greater pain improvement.

Recent reviews summarized the new therapeutic approaches for OA pain and highlighted the heterogeneous feature of OA pain [89, 90]. It is highlighted that treatments might be only effective for subsets patients with a specific phenotype. Targeting selected subgroup (phenotype) enables the development of more effective analgesic and reduces the suffering of ineffective treatments. Patients with a specific OA phenotype (such as BMLs) have received

targeted therapies [91]. Further, studies using stratification according to neuropathic pain mechanisms confirm the effectiveness in certain subgroups of patients, but there are no studies available targeting selected OA pain phenotype in the clinical practice [92]. Therefore, implementing individualized treatments into clinical setting based on phenotypes from the research community still need considerable efforts.

In conclusion

Despite the fact that pain in knee OA is multifactorial, peripheral, psychological and neurological factors are considered key phenotypic dimensions in the identification of pain phenotypes. Further understanding of these factors contributing to OA pain mechanisms will lead to the identification of pain phenotypes in OA patients, thus ultimately provide individualised interventions.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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