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Review

Pain-phenotyping in osteoarthritis: Current concepts, evidence, and considerations towards a comprehensive framework for assessment and treatment

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ABSTRACT

Objectives: Pain as central symptom of osteoarthritis (OA) needs to be addressed as part of successful treatment. The assessment of pain as feature of disease or outcome in clinical practice and drug development remains a challenge due to its multidimensionality and the plethora of confounders. This article aims at providing insights into our understanding of OA pain-phenotypes and suggests a framework for systematic and comprehensive assessments.

Methods: This narrative review is based on a search of current literature for various combinations of the search terms "pain-phenotype" and "knee OA" and summarizes current knowledge on OA pain-phenotypes, putting OA pain and its assessment into perspective of current research efforts.

Results: Pain is a complex phenomenon, not necessarily associated with tissue damage. Various pain-phenotypes have been described in knee OA. Among those, a phenotype with high pain levels not necessarily matching structural changes and a phenotype with low pain levels and impact are relatively consistent. Further subgroups can be differentiated based on patient reported outcome measures, assessments of comorbidities, anxiety and depression, sleep, activity and objective measures such as quantitative sensory testing.

Conclusions: The complexity of both OA as disease and pain in OA prompt the definition of a set of variables that facilitate assessments comparable across studies to maximize our understanding of pain, as central concern for the patient.

1. Introduction

Osteoarthritis (OA) is a complex multifactorial disease and global health care challenge affecting more than 500 million people [1]. Not only is OA a major cause of reduction in quality of life and activities of daily living, with substantial socio-economic impact [2,3], but has also been associated with increased mortality [4]. Total joint replacement is typically the 'last resort', but approximately 20 % of patients remain

Abbreviations: ADAMTS5, A disintegrin and metalloproteinase with thrombospondin motifs 5; CPM, Conditioned pain modulation; FDA, Food and drug administration; NGF, Nerve growth factor; NMDA, N-methyl-d-aspartate; OA, Osteoarthritis; PRO, Patient reported outcome; QST, Quantitative sensory testing; PPT, Pressure pain thresholds; TS, Temporal summation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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symptomatic after the procedure [5]. In the absence of treatments that can halt or reverse the OA process, and despite much research over decades, there remains a huge unmet medical need.

For a "treatment of OA" claim for a medication that targets the underlying pathophysiology, regulatory authorities require benefits on how patients feel, function or (their joints) survive [6]. While structural changes are objectively quantifiable, validly assessing non-structural outcomes (i.e., pain or function) remains complex.

Previous research has established the concept of OA-phenotypes [7,8], i.e., the existence of observable patient characteristics that systematically differ between groups of patients affected by OA. Phenotyping thereby allows a stratification of a heterogeneous patient population and may be reflective of different underlying pathologic mechanisms defining different endotypes [9,10]. The existence of different OA pain-phenotypes [11] adds an additional layer of complexity.

This narrative review aims at summarizing key concepts of pain-phenotyping, presenting current evidence. Pain is the most important symptom of OA and its treatment central to patients' well-being. The manuscript tries to capture the complexity of OA-pain that underlines the need for personalized and targeted management approaches based on a better understanding of pain-phenotypes and underlying mechanisms. We argue that a better understanding of these aspects is crucial for designing meaningful future trials and measuring treatment success. The ultimate goal is to establish a framework for systematic and comparable pain assessments in OA patients, with the intention of developing and allocating targeted treatments that meet patients' and societies' expectations.

2. Pathophysiology of pain in OA

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [12]. This definition underlines the complex interaction of pain triggers with biological, psychological and social factors (see Supplementary Table 1) [13]. This definition also makes abundantly clear that the absence of a structural correlate does not disqualify a sensation as pain, and that pain can persist despite the normalization of structure. It remains unclear why or which patients transition from acute to persistent or chronic pain [14]. In principle, chronicity should be assumed in most OA patients with a typical pain duration of >6 months; indeed a "chronic pain" phenotype is consistently reported [15,16].

Pain perception, processing and transition to chronic pain are the result of experience-driven neuro-structural changes [17], neuro-immunologic crosstalk [18,19] and (epi)genetic mechanisms [20,21]. In principle, pain perception occurs in several "morphologic layers". Peripheral joint nociceptors are activated by mechanical, thermal or chemical stimuli such as cytokines or chemokines released as part of inflammatory processes and cartilage degradation in OA. This can also trigger vascularization and ingrowth of additional nociceptors perpetuating the stimulus [22]. Continuous or repetitive stimulation of nociceptors can reduce activation thresholds leading to peripheral sensitization with primary hyperalgesia (an abnormally increased sensitivity to pain at the site of tissue damage) or allodynia (pain from otherwise non-noxious stimuli such as light touch), which may be present in OA [16]. Nociceptor activity is transmitted via C-fibers (slow, burning pain) or A-delta fibers (fast, sharp pain) to the cell body situated in the dorsal root ganglion of the spinal cord. The activity is further transmitted to higher systems, whereas inhibitory and excitatory influences from the local cellular environment as well as thalamic centers, brainstem and cerebral cortex modulate the pain perception [17,23], explaining the interrelation between pain and affect [17,24], but also the impact from expectation, observed in placebo and nocebo phenomena [25,26].

Based on the above mechanisms, primarily three types of pain have been discerned (with some overlap) in OA:

I) Nociceptive pain is triggered by tissue damage and often responsive to NSAIDs [27]. Pain in OA was thought to be purely nociceptive [28] with inflammation as potential pathophysiologic trigger and driver of pain [29,30]. The innate immune system [31], and especially macrophages play crucial roles in knee OA-pain through induction of inflammatory mediators [32], growth factors [33] and proteinases [34], and are reciprocally stimulated via nociceptor-secreted neuropeptides [35]. They also impact pain processing at the level of dorsal root ganglia and literature supports their role in pain sensitization and neuropathic pain [36,37]. Preclinical animal models evaluating anti-ADAMTS5 (a disintegrin and metalloproteinase with thrombospondin motifs 5) [38], or antibodies targeting Toll-like Receptors [39,40] in knee OA support the idea of neuroinflammatory mechanisms in OA-pain. Similarly, the neurotrophin NGF (nerve growth factor) has been implicated in OA-pain and inflammation [33,41]. NGF is increased in OA joints and promising clinical results for pain relief have been reported in humans and animals [42–44]. NGF is released in response to mechanical stress and inflammation [45], its role in the context of inflammation however is not fully understood yet [46], which may explain the safety concerns that finally led to a negative benefit risk evaluation for an anti-NGF antibody by the FDA (food and drug administration) [47]. In addition, histamine receptors have been implicated in nociception and chronic pain. Subtypes are expressed in the peripheral and central nervous system and play a role in the modulation of nociceptive transmission [48].

II) Nociplastic pain is a result of central dysregulation and sensitization, and refers to "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (IASP (International Association for the Study of Pain) definition) [12,49,50]. Yet, links between disease duration and measures of central sensitization seem weak [51] and most patients improve markedly after joint replacement, suggesting a peripheral driver of the pain experience [52].

Nociplastic pain is decoupled from the pathology at the joint level though also associated with neuroimmunologic changes. In view of the impact of central pain modulation, treatments such as patient education, sleep hygiene, and psychological treatment [53] or, centrally acting substances such as NMDA (N-methyl-D-aspartate) antagonists [53], cannabis-based medicines [54], tricyclic antidepressants, 5-hydroxytryptamine–noradrenaline reuptake inhibitors and gabapentinoids [53,55] may be beneficial as adjuncts in improving this type of pain. Similarly, sympatholytics may be beneficial in nociplastic and possibly neuropathic pain [53].

III) Neuropathic pain is typically associated with structural nerve damage [56], the morphologic correlate of which currently remains elusive in OA and may be related to comorbidities rather than OA (e.g., diabetes, lumbar radiculopathy, etc.). A recent matched pair approach in a cohort of knee OA patients suggested a potential neuropathic pain component in 8.2 % (based on PainDETECT). These patients differed from their likely non-neuropathic counterparts (matched for pain intensity) in having a higher degree of functional impairment and more painful joints but generally less pronounced radiographic joint changes [57].

3. Methods

This narrative review is based on a non-systematic search of current literature in Ovid MEDLINE® using the search terms "pain-phenotype" and "knee osteoarthritis" in various combinations to identify articles covering the area of interest. To evaluate potential surrogate measures for pain-phenotypes PubMed ® was searched for biomarkers evaluated in the context of OA. The search was then expanded to cross-referenced biomarkers and interventions.

4. Studies examining knee OA pain-phenotypes

The relevance of the different mechanisms for pain perception in OA underlines the importance of distinguishing the predominant pain type

or mechanism for a successful treatment allocation especially in relation to nociceptive vs non-nociceptive pain. This distinction can be achieved via pain-phenotyping, i.e., the differentiation of patient clusters based on observable traits associated with differences in pain experience.

Various studies have used phenotyping approaches to characterize pain-phenotypes in OA as summarized in Table 1. Murphy et al. [58] cross-sectionally evaluated the co-occurrence of centrally mediated symptoms in older adults with hip or knee OA and identified three pain-phenotypes. Those with the highest pain levels also showed high levels of depression and fatigue, low sleep quality and a high burden of comorbidities potentially indicating a higher overall impact from central mechanisms of pain perception. Patients in this cluster had the highest disease impact on health-related quality of life. The second cluster had intermediate levels of depression and fatigue, low levels of pain and good sleep, possibly indicative of a mixed peripheral and central pain-phenotype. The third cluster had overall low levels of pain, fatigue or depression, but a poor sleep quality. This could be patients with a predominantly nociceptive pain type [58]. However, because this evaluation was cross-sectional, directionality and mechanisms cannot be discerned.

Finan et al. [59] also evaluated patient reported outcome (PRO) information on anxiety/depression symptoms, sleep and pain catastrophizing but included the congruence between pain and structural changes versus quantitative sensory testing (QST). They dichotomized pain (cut-off 4.22 out of 20 on WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain subscale score) and radiographic grade (Kellgren-Lawrence 1 and 2 vs. 3 and 4) resulting in four combinations. The high-pain groups trended towards higher impact in psychosocial function, which was significant for patients with high-pain and low radiographic grade. The most notable finding was that the high-pain and low-Kellgren-Lawrence group exhibited hypersensitivity on several QST modalities at unaffected anatomic sites, suggesting a propensity towards central pain sensitization. In contrast, the other discordant group with low-pain and high-Kellgren-Lawrence were the least pain-sensitive [59].

Similarly, Egsgaard et al. [60] aimed at identifying pain profiles in patients with OA based on psychological measures, QST, Kellgren-Lawrence grade and biomarkers. Compared to controls, the four resultant clusters had higher disease impact on physical functioning, quality of life and pain response. In the order of pain impact (low to high), the cluster of patients with overall low pain sensitivity and higher CPM (conditioned pain modulation) than controls had the lowest pain. The next lowest pain cluster showed increased temporal summation at the arm only (TS) with CPM and pressure pain thresholds (PPT) comparable to controls, potentially indicative of an early stage of chronification. Two clusters showed reduced PPTs, enhanced TS and reduced CPM. In addition, one of those clusters was characterized by greater hyperalgesia, lower general health and pain catastrophizing. While both of these clusters showed alterations in pain thresholds quantifiable with QST, the one additionally affected by lower general health and pain catastrophizing reported the highest values on the three WOMAC subscales, suggesting an additive effect on pain experience [60].

In addition to psychological measures, radiographic OA grade and patient characteristics, Kittelson et al. included extensor strength in their approach to pain-phenotyping of the OAI (osteoarthritis initiative) database [61], as well as a community sample that comprised participants with symptomatic OA and healthy older adults as controls [62]. In both samples they identified four pain-phenotypes, one primarily characterized by a high burden of comorbidities, one by a high level of psychological distress and pain, and one with high extensor strength and a low overall burden of disease. Participants from the community sample in this latter group often had a history of knee trauma or surgery [62]. A fourth pain-phenotype was identified in both analyses; in the OAI, this fourth phenotype was characterized by a high proportion of joint line and pes anserine tenderness [61]. In the community sample, the fourth phenotype was differentiated by low target knee PPTs [62].

Reducing heterogeneity due to differences in OA severity, Frey-Law et al. [63] analyzed pain-phenotypes in patients scheduled for knee arthroplasty and identified five phenotypes based on psychological assessments, patient characteristics, QST, pain characteristics, function and quality of life. One pain-phenotype exhibited low pain sensitivity but high PPTs at the target knee. Another exhibited average pain sensitivity to all tested stimuli. In contrast, three clusters showed high sensitivity to pain. These three clusters differed in their sensitivity to TS, heat and pressure pain, and punctate pain, respectively. There was no relevant impact from the other evaluated characteristics except a predominance of males in the low pain group. Interestingly, in the high pain sensitivity group, high punctate and high heat and pressure pain sensitivity translated into higher clinical pain levels, while TS did not [63].

Evaluating thermal measures of QST as potential indicators of central sensitization and neuropathic pain and their correlation with pain levels, pain characteristics and function, Wright et al. [64] compared a community sample of patients with painful knee OA to pain-free volunteers. Patients with OA displayed lower PPTs than pain-free volunteers at the index knee but not at other sites. In addition, patients with OA showed cold pressure pain on average at higher temperatures than pain-free controls at the index and contralateral knee, as well as a distant site. This cold hyperalgesia was pronounced in a subgroup of 44 % of patients. These patients also had a tendency towards reduced thresholds for pressure and thermal pain at sites other than the target knee, higher pain levels, higher functional impact and higher PainDETECT scores. Despite the differences in QST between the groups, there were no differences in psychological impact [64].

In the only longitudinal study to date to assess pain susceptibility by Carlesso et al. [65], four distinct phenotypes were identified among people with or at risk of knee OA who were free of persistent knee pain at baseline. Interestingly, the group that was the most sensitized based upon PPT measures had a two-fold higher risk of developing persistent knee pain compared with the group that had the least sensitization based upon PPT and TS. Further, the group that exhibited TS was not at increased risk for developing persistent knee pain [65]. The other factors that were examined (i.e., widespread pain, pain catastrophizing, depressive symptoms, poor sleep) did not differentiate between the groups, and thus did not contribute to risk of developing persistent knee pain.

Heat and cold hyperalgesia have recently further been evaluated by Carlesso et al. [66] in an analysis of pain-phenotypes in patients presenting with knee OA. The analysis was based on the IMMPACT recommendations for pain-phenotyping, i.e., "pain variability, intensity and qualities, somatization, anxio-depressive symptoms, sleep, fatigue, pain catastrophizing, neuropathic pain, and quantitative sensory tests" [67]. The three pain classes separated based on PRO information (consistent high, intermediate or low disease impact). The results for QST were less clear. Temperature sensitivity and PPTs separated the least affected from the two other classes. Only TS was significantly different for all the classes [66]. TS has also been demonstrated to separate clusters in other cohorts [59,60,63,65], and to potentially predict acute postoperative pain intensity and chronic postsurgical pain [68,69].

Two studies evaluated clinical pain-phenotyping and included imaging. In a community sample of older adults, Pan et al. identified three subgroups of patients with knee pain [70]. A predominantly female class including patients with high local pain, a high burden of emotional problems and limited structural changes was identified, while another class was dominated by males with low disease impact but definite structural changes. The third class was healthy overall with limited signs of structural OA and low levels of knee pain, assumed by the authors to comprise participants with early OA. Pain levels between the high and low pain groups consistently differed over 10.7 years and were not necessarily correlated with the presence of radiographic signs of OA.

In another cohort study of community dwelling adults, Burston et al. [71] evaluated the impact of anxiety and depression on incident knee pain. They report an odds ratio (OR) of 1.71 for incident knee pain at twelve months in individuals with baseline anxiety (adjusted for

Table 1
Summary of key OA pain-phenotyping studies.

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Murphy et al. [58] 2011	older adults (≥65y) with hip or knee OA and signs of primary fatigue	129 (69 % knee OA)	relationship among pain, fatigue, and physical activity	na	Hierarchical agglomerative cluster analysis Cross sectional Community sample	**Patient Characteristics**	61 % female Age: 72.2 (±9.8), range 65–90 y BMI: 30.5± 5.9 kg/m^2, range 21.5–49.9 Self-reported duration of pain (months) 132.1 (146.5) range 0–708	no significant differences in patient characteristics
						Brief Fatigue Inventory	BFI total 4.5 (2.0) range 0.25–8.75	**Cluster I:** 36 % highest scores on all measures - high stiffness, high disability, TUG 13.5±8.9
						WOMAC	WOMAC pain 7.9 (3.4) range 2–20 WOMAC stiffness 3.3 (1.7) range 0–8 WOMAC disability 20.9 (10.3) range 3–42	**Cluster II:** 30 % subclinical depression, moderate fatigue, moderate illness burden, overall low pain, low sleep disturbance - stiffness moderate, disability low, TUG 10.5± 2.1 s
						- 5 times daily NRS pain assessment - Illness burden (41 somatic symptoms) - Timed up-and-go test - Activity measured via Actiwatch - Pittsburgh Sleep Quality Index (PSQI) - Center for Epidemiologic Studies Depression Scale (CES-D)		**Cluster III:** 34 % relevant sleep disturbance, mild pain, low fatigue and depression scores, low illness burden - low stiffness, moderate disability, TUG 10.2±2.3s
Finan et al. [59] 2013	Baseline of study to evaluate psychological treatments in OA patients with/without insomnia	113	Association between self-reported levels of pain with measures of central sensitization in the absence of moderate-to-severe radiographic evidence of pathologic changes of knee OA	na.	cross-sectional multivariate general linear modeling	**Patient Characteristics**	66.7 % female Age: 61.05±8.93 y BMI: 30.94±5.85 kg/m^2	**Low pain/low knee OA grade (21.2 %):** overall lowest BMI **High pain/high knee OA grade (28.3 %):** reduced distant (and local) PPT vs low pain groups, high rate of depression, anxiety, sleep disturbance and pain catastrophizing, overall highest BMI **Low pain/high knee OA grade (23.90 %):** overall oldest group **High pain/low knee OA grade (26.5 %):** significantly increased pain response to distant mechanical phasic stimuli and thermal phasic pain compared to high knee OA groups, reduced distant PPT vs low pain groups, high rate of depression, anxiety, sleep disturbance and pain catastrophizing, overall youngest group
						• STAI • CES-D • PCS • PSQI • Radiographic disease severity (Kellgren/ Lawrence) • QST • *PPT* • *CPT* • *Mechanical phasic pain* • *Thermal phasic pain*		

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Table 1 (*continued*)

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
						• *Sensitivity to tonic pain* • *CPM*		**no differences in CPM or QST measures locally, education and income as significant covariates**
Egsgaard [60] et al. 2015	full spectrum from no clinical OA to clinical OA, randomly selected from pre-existing database 40-80y controls with no OA and little or no pain	280 (216:64)	identification of knee pain profiles identification of marker patterns correlating to pain profiles	non-OA knees largely independent of pain	Principal Components Analysis (PCA) with clustering using Ward's method with squared Euclidean distance	**Patient Characteristics** • OA grade • Comorbidities • Number of painful joints • Pain duration • Pain localization • WOMAC • Lequesne functional index • EQ-5D • Pain catastrophizing • QST • *PPT* • *TS* • *CPM* • Biomarkers • VICM • CIM • CRP • CRPM • CIIIM	64 % female Age: 61.7±10.0 y BMI: 33.9±7.0 kg/m^2	**Principal components:** PC1: physical health questionnaires PC2: peripheral, central, and spreading sensitization, PC3: biochemical markers, PC4: pain catastrophizing, PC5: temporal summation. **Profile A (12.5 %):** moderate impact on WOMAC/Lequesne, low to moderate catastrophizing, near normal TS, high CPM and PPT as potential sign of resilience, still reduced QoL **Profile B (27.3 %):** moderate impact on WOMAC/Lequesne, low to moderate catastrophizing, near normal TS, moderate CPM but reduced PPT, reduced QoL **Profile C (39.4 %):** moderate impact on WOMAC/Lequesne, low to moderate catastrophizing, increased TS, reduced CPM and PPT, reduced QoL, CRP near normal **Profile D (18.9 %):** higher impact on WOMAC and especially Lequesne, increased catastrophizing, increased TS, reduced CPM and PPT, reduced QoL **Profile E (1.9 %):** outlier cluster, not reported in detail **controls low impact on WOMAC/Lequesne, moderate CPM and PPT, low TS**
Kittelson et al. [61] 2016	OAI from the incident and progression cohort	3494	Knee OA pain-phenotypes based on 1) knee OA pathology 2) psychological distress 3) altered pain neurophysiology 4) relation to patient characteristics	na	Latent Class Analysis cross sectional cluster analysis (4-year follow-up visit) with some longitudinal information	**Patient Characteristics** • Numeric Pain Rating Scale (NPRS)	OA 59.2 % female Age: 64.9± 9.0 y BMI: 28.9±5.0 kg/m^2 similar symptom duration and	**Class 1:** on average older than all other classes, higher proportion of females, slowest walking speed, high level of comorbidities **Class 2:** on average older than class 3/4, high levels of knee joint tenderness, weak extensor strength and high proportion of pes anserine tenderness **Class 3:** highest pain level, psychological

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Table 1 (*continued*)

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
						• WOMAC • Radiographic severity of knee OA • MVIC • Tenderness of the knee joint • Modified Charlson Comorbidity Index • Number of pain sites (as surrogate for central sensitization) • CES-D • Modified version of the coping strategies questionnaire-catastrophizing subscale • 20-m timed walking test at self-selected walking speed • Health seeking behavior (unstructured question)	health seeking behavior	distress, highest number of painful sites and more severe radiographic OA **Class 4**: mild radiographic OA, low levels of pain and comorbidity, highest average extensor strength
Kittelson et al. [62] 2021	Recruitment from community (healthy elderly) and orthopaedic clinics (OA patients) 50-85y	183 (152:31)	Knee OA pain-phenotypes based on 1) multimorbidity 2) psychological distress 3) pain sensitivity 4) knee impairment or pathology	healthy community dwelling elders	Latent Profile Analysis Cross sectional Community sample	**Patient Characteristics** • Visual analog scale (VAS) • WOMAC pain • ICOAP • Normalized knee extensor strength at maximum voluntary isometric contraction (MVIC) • Functional Comorbidity Index (FCI) • Pain Catastrophizing Scale (PCS) • Walking speed • Health seeking behavior (unstructured question) • Symptom duration • QST • *PPT (target knee)* *Tampa Scale for Kinesiophobia, modified Charlson Comorbidity Index, PPT (regional/distant), Radiographic Severity of Knee Osteoarthritis, CES-D evaluated but excluded based on weaker correlation with pain intensity (Spearman correlations)*	OA 64.5 % female, control 64.5 % female Age: OA 65.2±8.5 y, control 64.9±9.0 y BMI: OA 30.2±6.0 kg/m^2, control 26.7±4.6 kg/m^2 similar symptom duration and health seeking behavior	**Group 1 (9 % of pt with knee pain):** characterized by high FCI scores (upper gastrointestinal, osteoporosis, heart disease, asthma), slower walking speed than group 2/4 (“weakness and heightened pain sensitivity with multimorbidity") **Group 2 (63 % of pt with knee pain):** low PCS and FCI (vs group 1 and 3), higher target knee PPT and lower extensor strength than healthy elderly or group 4 (“weakness and heightened pain sensitivity") Group 3 (11 % of pt with knee pain): characterized by pain catastrophizing, higher pain ratings than group 2/4 (“weakness and heightened pain sensitivity with pain associated distress") **Group 4 (17 % of pt with knee pain):** characterized by high PPT vs all other groups, otherwise similar to healthy elderly, highest proportion of pt with previous knee surgery or trauma (“normal strength, low pain sensitivity")

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Table 1 (*continued*)

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Frey-Law et al. [63] 2017	Baseline of TANK (TENS After New Knee) study NCT01364870 ≥30y scheduled for primary total knee joint replacement	218	QST pain sensitivity profiles in advanced knee OA	na	Principal Components Analysis (PCA) and Principal Axis Factoring (PAF) with clustering using Ward's method with squared Euclidean distance	**Patient Characteristics** • Pain intensity (rest and movement) via 21-point NRS • Pain duration • Analgesic medication • State-Trait Anxiety Inventory (STAI) anxiety subscale • Geriatric Depression Scale (GDS), 5-item version • PCS • KOOS • SF-36 • QST • *PPT* • *HPT and HPTol* • *Punctate Pain Intensity* via *VAS* • *TS* via *tonic heat stimulus*	54.6 % female (50 % in control group) Age: not reported BMI: not reported	**Low Pain Sensitivity Profile (18.3 %):** low QST based standardized pain sensitivity before and after adjustment for age and sex **Average Pain Sensitivity Profile (38.5 %):** average QST based standardized pain sensitivity, after adjustment for age and sex more pronounced difference in PPT and HPT vs low pain sensitivity cluster **High Pain Sensitivity Profile temporal summation (20.6 %):** isolated high TS with low values for other qualities, effect pronounced after adjustment **High Pain Sensitivity Profile high heat and pressure pain (17.9 %):** before adjustment, after adjustment similar to average pain sensitivity cluster with TS as main discriminator, higher pain levels than pure TS cluster also in KOOS, at rest, gait and range of movement **High Pain Sensitivity Profile high punctate pain (4.5 %):** average for all qualities also after adjustment except punctate pain with highest pain levels also in KOOS, at rest, gait and range of movement no relevant impact from other assessments apart from sex. Men were predominantly represented in low pain sensitivity cluster. After adjustment higher pain sensitivity for non-white and/or hispanic individuals
Wright et al. [64] 2017	adults with painful knee OA pain-free volunteers (≥50y)	120 (80:40)	widespread cold, pressure, and heat hyperalgesia in OA patients differences in QST measures, levels of pain, pain characteristics, and perceived function in patients with wide-spread cold hyperalgesia	pain free control OA patients with and without wide-spread cold hyperalgesia	Standard statistics Cross sectional Community sample	**Patient Characteristics**	OA 55 % female, control 60 % female Age: OA 64, range 50–86 y; control 64, range 51–86 y OA 38 % obese, control 10 % obese	no significant differences in patient characteristics

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Table 1 (*continued*)

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
						Brief Fatigue Inventory **WOMAC** **Short-Form Health Survey (SF-36)** • PainDETECT • Pain quality assessment scale (PQAS) • QST • *PPT* • *CDT* • *CPT* • *WDT* • *HPT*	BFI total 4.5 (2.0) range 0.25–8.75 OA WOMAC pain, 18.5/50 OA WOMAC function, 53.4/250 43.75 % (n = 35) cold hyperalgesic based on 12.25 °C cut off	**OA vs pain free:** sign. higher index knee PPT in OA (pressure hyperalgesia: 22.50 % index knee, 16.25 % contralat. knee, 3.75 % distant site) sign. higher CDT at index and contralat. knee (cold hypoesthesia 11.25 % index knee, 17.50 % contralat. knee, 17.50 % distant site; cold hyperalgesia 47.50 % index knee, 37.50 % contralat. knee, 43.75 % distant site) sign. higher overall WDT in OA, no differences in HPT (heat hypoesthesia 11.25 % index knee, 17.50 % contralat. knee, 17.50 % distant site; heat hyperalgesia 47.50 % index knee, 37.50 % contralat. knee, 43.75 % distant site) **Cold hyperalgesic vs non-hyperalgesic OA patients:** sign. lower cold detection and cold pain threshold at all sites cold-hyperalgesic vs non-cold hyperalgesic OA patients, no difference between non-hyperalgesic OA patients vs pain-free controls sign. lower warmth detection threshold at index knee and distant site (cold hyperalgesic patients vs all others), sign. lower warmth detection threshold at contralateral knee (cold hyperalgesic patients vs pain free controls, but not vs other OA patients), lower heat pain threshold at all sites (cold hyperalgesic patients vs other OA patients), but no difference between cold hyperalgesic patients and controls. sign. higher index knee and contralat knee PPT, no sign. difference at distant site no differences in SF36 based on cold hyperalgesia in OA patients, higher WOMAC pain and disability in patients with cold hyperalgesia, correlation between cold

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Table 1 (*continued*)

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
								hyperalgesia and PainDETECT scores and surface and paradoxical subscores in pain quality assessment scale
Pan et al. [70] 2019	Recruitment from community (healthy elderly) and orthopaedic clinics (OA patients) 50-85y	Tasmanian Older Adult Cohort Study	963	knee pain-phenotypes in an older population	Latent Class Analysis Cross sectional Community sample	**Patient Characteristics** • WOMAC pain • Number of painful sites • MRI characteristics (cartilage defects, bone marrow lesions, effusion-synovitis) • Radiographic presence of knee OA • Education level • Single mental health item from the short form-8 • 4-item comorbidity questionnaire (heart attack, diabetes, hypertension, rheumatoid arthritis)	50 % female (sampling strategy) Age: 62.8±7.4 y BMI: 27.7±4.6 kg/m^2	**Class 1 (25 %):** highest proportion of females, on average more emotional problems, higher burden of comorbidity, more severe knee pain and more painful sites, lower knee structural damage, lower education **Class 2 (20 %):** more males, higher level of education, fewer painful sites or structural knee abnormalities, lower levels of pain **Class 3 (50 %):** overall lowest prevalence of knee pain, comorbidities, radiographic OA, structural damage and low BMI **consistently WOMAC and painful sites Class 1 > Class 2 > Class 3 over average 10.7 y**
Burston et al. [71] 2019	participants from a community-based cohort study ≥40y	230 (130:100) 3274 for impact of anxiety (351 anxiety at baseline) on incident knee pain at 12 months 3767 for impact of knee pain (1020 with baseline knee pain) on incident anxiety at 12 months	associations between knee pain, pain spread, anxiety, and depression	Non-OA patients	Spearman correlation and linear regression	**Patient Characteristics** • HADS • Intermittent and Constant Osteoarthritis Pain scale (ICOAP) • Numeric Rating Scale (NRS) • OA severity (Kellgren-Lawrence) • QST • *PPT*	OA 61.9 % female, control 58.2 % female Age: OA 60.27±9.61 y; control 63.06, ± 8.88 y BMI: OA 27.1±4.56 kg/m^2, control 30.09±6.62 kg/m^2	**Impact of anxiety (25 % of population)** anxiety sign. associated with all pain measures and PPTs after adj. for depression odds ratio (OR) for incident knee pain at 12 months in patients with anxiety 1.71 (adj. for depression) OR for incident anxiety at 12 months in patients with knee pain 1.18 (after adj. for depression) OR for incident anxiety at 12 months in patients with depression 3.20 **Impact of depression (10 % of population)** OR for incident knee pain at 12 months in patients with depression 1.66 (adj. for anxiety)

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Table 1 (*continued*)

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Carlesso et al. [65] 2019	MOST population 50-79y having/at risk of developing knee OA without persistent knee pain	852	pain susceptibility phenotype (PSP) based on development of persistent pain at 2 years	na	Latent Class Analysis observational longitudinal	**Patient Characteristics** • Widespread pain index (WPI) • QST • *PPT* • *TS* • Coping Strategies Questionnaire (single item for pain catastrophizing) • - CES-D	55 % female Age: 67y BMI: 29.5 kg/m^2	**Pain susceptibility phenotype (PSP)** **PSP 1 (34 %):** pressure pain sensitivity (~16–26 %), facilitated TS (33–35 %) **PSP 2 (31 %):** pressure pain sensitivity (0–6%), facilitated TS (2–10 %), 22 % non-caucasian **PSP 3 (23 %):** pressure pain sensitivity (75–89 %), facilitated TS (53–58 %), 74 % female, higher risk of developing incident knee pain **PSP 4 (12 %):** pressure pain sensitivity (0–4%), facilitated TS (82–90 %), 26 % female, 23 % non-caucasian, mean age 70 % **no relevant differences in other aspects analyzed**
Carlesso et al. [66] 2022	orthopaedic specialist confirmed diagnosis of OA ≥40y	343	Pain-phenotype identification based on IMMPACT criteria	na	Latent Class Analysis observational longitudinal	Patient Characteristics • Modified Pain Detect Questionnaire • Hospital Anxiety and Depression Scale (HADS) • Patient Health Questionnaire-15 (self- administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument) • Pain Catastrophizing Scale • Multidimensional Fatigue Inventory • Pain variability (NRS 3 times via text for a week) • Average pain intensity (NRS, recall 1 week) • Pittsburgh Sleep Quality Index (PSQI) • Short form McGill Pain Questionnaire 2 • QST • *PPT* • *TS* • *CPT* • *HPT* • *CPM* (Conditioned pain modulation) • Self-report Charlson comorbidity index	63 % female Age: 64y BMI: 32 kg/m^2	**Class 1 (49 %):** overall low scores in all assessed measures (i.e. low severity) or marginal signs of central sensitization according to QST **Class 2 (40 %):** overall moderate scores in assessed measures, but high pain variability, mixed QST values **Class 3 (11 %):** overall highest scores in assessed measures (except pain variability), QST values for PPT patella, TS, cold pain and CPM heat pain as indicator of relevant central sensitization **decreasing function from class 1 to class 3 considering walk fast and climb stairs, no significant difference for sit stand increasing health care utilization of 44 % and 240 % for class 2 and 3 respectively compared to class 1**

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Table 1 (*continued*)

Reference	Population	Sample Size (for comparative studies n of OA patients: n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
						• Life Orientation Test- Revised scale (dispositional optimism) • Chronic Pain Self Efficacy Scale • Kellgren-Lawrence grade • Knee Injury and Osteoarthritis Outcomes Score (KOOS) activities of daily living subscale • Core measures of functional performance (1) transition from sit to stand, 2) walk fast and 3) climb stairs • Healthcare Utilization (via provincial insurance system in one vicinity)		

Abbreviations: pt: patients; BMI: Body Mass Index; BFI: Brief Fatigue Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; FCI: Functional Comorbidity Index; GDS: Geriatric Depression Scale HADS: Hospital Anxiety and Depression Scale; ICOAP: Intermittent and Constant Osteoarthritis Pain scale KOOS: Knee Injury and Osteoarthritis Outcomes Score; MVIC: Normalized knee extensor strength at maximum voluntary isometric contraction; NRS: Numeric Rating Scale; NPRS: Numeric Pain Rating Scale PCS: Pain Catastrophizing Scale; PRIME-MD: Primary Care Evaluation of Mental Disorders; PQAS: Pain quality assessment scale; PSQI: Pittsburgh Sleep Quality Index; SF-36: Short-Form Health Survey; STAI: State-Trait Anxiety Inventory; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; QST: Quantitative Sensory Testing; CDT: Cold Detection Threshold; CPT: Cold Pain Threshold; CPM: Conditioned pain modulation; HPT: Heat Pain Threshold; HPTol: Heat Pain Tolerance; PPT: Pressure Pain Threshold; TS: Temporal Summation; WDT: Warmth Detection Threshold; CIM: Collagen I Metabolite; CIIIM: Sollagen III Metabolite; CRP: C-Reactive Protein; CRPM: C-Reactive Protein Metabolite; VICM: Citrullinated Vimentin Fragment.

depression), and a 1.66 OR in patients with baseline depression (adjusted for anxiety). These insights complement a preclinical OA model that demonstrated astrocyte activation as potential correlate of altered pain perception in animals with elevated baseline anxiety-like behavior reversible after introducing a centrally acting anxiolytic [71].

In summary, the above-described studies clearly demonstrate the existence of several OA pain-phenotypes, which seem differentiable based on objective measures and PRO information. Many approaches suggest a low pain-phenotype as well as a phenotype with high pain perception and impact. Interestingly, few articles on OA and OA pain-phenotypes specifically report pes anserine tenderness [61,72,73], which may confound OA-pain perception and OA pain-phenotyping.

Furthermore, the observed differences and similarities in previous OA-phenotyping analyses underline the importance of the choice of input variables for the allocation of clusters in phenotyping [72]. The observed differences in pain perception and pain-phenotypes do not necessarily correlate with the extent of radiographic changes. There seems to be a certain overlap between structural OA and OA pain-phenotypes if imaging is included as an input variable [61,62,70,72]. Whether imaging information dominates differences between phenotypes, or if pain-phenotypes are associated with structural changes assessed on imaging merits further investigation.

To further differentiate pain-phenotypes, the degree of altered neurobiological signalling appears to be particularly relevant; specific questionnaires and QST measures, especially TS and PPTs or thermal sensitivity appear to be important.

4.1. Limitations of existing tools to identify OA pain-phenotypes

Pain measurement in OA studies primarily focuses on questionnaires that inquire about the intensity, pain on movement and a limited range of pain characteristics to capture the pain experience (Supplementary Table 1). However, most of these questionnaires do not differentiate the underlying pain mechanism(s) at play in any given individual. Further highlighting the complexity of OA, numerous biomarkers (as potential indicators of pathophysiologic mechanisms in OA) and interventions have been evaluated in the context of structural and symptom (pain) OA outcomes (Supplemental Table 2). Patients with different pain-pheno- and -endotypes may report similar pain intensity and dimensions. These pain measures therefore may not be suitable to categorize patients but should be used as outcome measures to explore treatment effects. To identify different pain-pheno- and -endotypes, assessments should include clinical/biological information as well as medical history (e.g., burden of comorbidities, signs of dysfunctional pain experience or pain quality, sleep, anxiety and depression, physical activity and assessment of somatosensory function by QST, see Supplemental Table 3). Given the above-described convergence of structural OA and OA pain-phenotypes if imaging or performance measures are added to the clustering, the selection of input variables has to be carefully considered.

Comorbidity impacts pain [74] and various measures are used to estimate the burden of comorbidity (comprehensively summarized by Stirland et al. [75]). It is however vital to consider a score's "original purpose and the outcomes for which it is validated" [75]. Scores

developed to predict mortality (e.g., Charlson Comorbidity Index) may be unsuitable to reflect the burden of comorbidity and its impact on physical functioning.

Affective states such as anxiety, depression or pain catastrophizing influence pain modulation and perception of pain. While there are diagnostic criteria and tools to identify and grade anxiety and depression, a consensus regarding how to measure catastrophizing has not yet been reached [76]. Measures of emotional dysregulation or positive and negative affect can also be useful [77,78]. Kinesiophobia has been reported as predictor of disability impacting quality of life in various pain conditions; it has been associated with chronic pain and thus may also present a useful addition [79,80].

Exercise can positively influence pain [81]; pain and activity may have a reciprocal relationship in some individuals; it may therefore be misleading to assess one without the other [82,83]. This results in methodologic challenges. Objective performance tests are subject to day-to-day variability and reflect what patients are able to do under observation rather than what they habitually do in their free-living environment. The domain of activity, in the future, may best be captured using digital devices that allow the measurement of indicators in the free-living environment like step count, activities at a certain heart rate or radius of mobility. Similarly, objective assessment of sleep structure may be obtained using wearable technology [84,85]. Measuring elements of sleep is increasingly recognized as an important aspect to understanding the pain experience since sleep and pain are also closely inter-related; pain may disrupt sleep, and sleep disturbance negatively impacts descending pain inhibitory pathways, heightens pain sensitivity and attenuates opioid analgesia [84,86–88]. These examples underline the importance of systematically assessing pain and potential confounders in an integrative approach.

5. Considerations for a broader collection of pain measures

This summary highlights the complexity of the pain experience as multidimensional physical and psychological phenomenon, as well as of the plethora of assessment tools. It also suggests the existence of different patterns of observable traits, OA pain-phenotypes, which likely reflect different underlying mechanisms contributing to the overall pain experience. Striving for the development of a personalized and targeted management of OA, pain is a critical factor, and central to patients' well-being. OA-pain is associated with multiple pathophysiological mechanisms reflected in distinct pheno- and endotypes. This implies the need to systematically define those pain-pheno- and -endotypes independent of the underlying OA pheno- and -endotype.

We therefore suggest the systematic collection of additional pain-related data, such as pain quality, including potential signs of sensitization and other altered neurobiological mechanisms, burden of comorbidity, presence of anxio-depressive psychopathology, sleep quality and physical activity as a minimal set of assessments. Other aspects such as pain catastrophizing, kinesiophobia, dysregulation of affect, etc. may play an important role. At the moment there is however less consensus about their independent relevance and optimal tools for the assessment of these concepts. Similarly, the potential application of this additional pain-related data necessitates further evaluation. The individual use of the PRO information could lead to unnecessary fragmentation of the patient population. The use of patient response or patient characteristics patterns in form of phenotypes for subgroup analyses or treatment allocation though could support drug development. Pain-phenotyping could be specifically valuable to discriminate treatments without any effect on pain, from those that target specific pain processes.

QST allows valuable additional insights into pain processing. Necessary expertise, equipment and time for valid assessments may be challenging, thereby impacting the implementability of comprehensive QST protocols in large multicenter trials. Nevertheless, future research may guide the construction of targeted somatosensory assessment-batteries based on their discriminative value e.g., in combination with PROs, which would allow a broad implementation and add relevant scientific value to OA trials.

One challenge has been the comparability of various PROs that focus on slightly different clinical domains. Georgopoulous et al. have recently demonstrated, that harmonized results of the 4 most widely used PROs for pain assessment produce similar patient acceptable symptom states and are thus comparable [89]. To increase our knowledge about pain-phenotypes from published and future studies, a similar concept to generally interpret and compare PRO results could be applied, leveraging established cut off values [71]. Alternatively cut-off values such as tertiles or quartiles of the original score range could be used [65]. The latter approach is based on the assumption, that for a score e.g., ranging from 0 to 100 with 100 denoting high impact from a given pathology, people who score between 0 and 25 or 0–33 are less likely to be impacted, compared to those scoring between 66 and 100 or 75–100. While on a granular level, the different scores may convey different nuances of patient experience (and thus allow focus in a specific project), a separation in tertiles or quartiles in principle allows the clear identification of highly vs marginally affected individuals for comparison with other studies. This could also facilitate the implementation of systematic PRO-based assessments in clinical practice to allow individualized treatment approaches.

The legacy of numerous failed trials, the increasing cost pressure on healthcare systems, and the public and individual health burden of OA are concerning. Given the increase in mechanistic understanding, the field is under a certain pressure to develop medicines that address patients' symptoms and halt or reverse OA. One prerequisite for the development of worthwhile treatments is the establishment of clinical endpoints that provide a meaningful reflection of disease modification and long-term patient benefit. This can only be accomplished if we better understand and measure pain in OA which could also give further insights in the pain structure relationship. However, to achieve real progress, data need to be comparable. Systematic generation of data that allow OA pain-phenotyping may be one piece of the puzzle towards a "treatment of OA".

Author contributions

AH and FS have collected the information for the tables and performed literature research. All authors have been involved in the analysis and interpretation of the data and contributed to the final manuscript.

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Declaration of competing interest

Franziska Saxer is employee and shareholder of Novartis, she is affiliated to the University Basel and member of the European Union Medical Devices - Expert Panel section Orthopaedics, traumatology, rehabilitation, rheumatology.

Alexa Hollinger is a medical fellow at Novartis, she is affiliated with the University Hospital Basel and the University of Basel.

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Appendix A. Supplementary data

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