
Structural correlates of pain in osteoarthritis

T. Neogi

Boston University School of Medicine and
School of Public Health, Boston, USA.

Tuhina Neogi, MD, PhD, FRCPC

Please address correspondence to:

Dr Tuhina Neogi,

Boston University School of Medicine,

650 Albany Street

Clin Epi Unit, Suite X200,

Boston 02118, MA, USA.

E-mail: tneogi@bu.edu

Received and accepted on September 1,
2017.

Clin Exp Rheumatol 2017; 35 (Suppl. 107):
S75-S78.

© Copyright CLINICAL AND

EXPERIMENTAL RHEUMATOLOGY 2017.

Key words: osteoarthritis, pain,
structure, synovitis, effusion,
bone marrow lesions, sensitisation

ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis, with knee OA itself being among the most common conditions and a leading cause of disability among older adults worldwide. Pain is a key symptom in the decision to seek medical attention, yet available therapies for managing OA are limited with only minimal or moderate efficacy. Current approaches to pain management in OA have been rather non-specific, limited to acetaminophen or NSAIDs primarily, without targeting underlying structural lesions that may be contributing to pain in OA. With the advent of MRI, a number of studies have noted the importance of bone marrow lesions and synovitis/effusion to the pain experience in OA. These pathologic features are therefore attractive treatment targets, with some proof-of-concept studies demonstrating the potential efficacy of targeting these lesions. Another increasingly recognised important contribution to pain in OA is sensitisation, which is associated with pain severity. Synovitis/effusion have been identified as potentially leading to development and worsening of sensitisation. Much work remains to be done in understanding the mechanisms by which structural pathology causes pain; such insights are urgently needed to develop new treatment approaches to help millions of people worldwide who are burdened by pain from OA.

Introduction

Musculoskeletal pain is common, with joint pain being the most commonly reported type of pain among US adults (Fig. 1). Osteoarthritis (OA) is the most common joint disorder, with knee OA being among the most common musculoskeletal conditions worldwide (Fig. 2), estimated to affect 250 million (1). Overall, approximately 10–12% of the adult population have symptomatic OA of any joint (2, 3). From 1995 to 2005, the number affected with clinical OA grew from 21 million to nearly 27

million in the US, and is expected to continue to rise with the aging of the population and prevalence of obesity (4, 5). Knee OA is particularly burdensome as a leading cause of disability among older adults, accounting for a greater risk of mobility disability than any other medical condition in people aged 65 and over (6, 7). Pain from knee OA is a key symptom in the decision to seek medical care and an important antecedent to disability. With no therapies available proven to alter structural progression, treatment is aimed primarily at ameliorating symptoms, yet symptomatic management is poor, with only minimally or moderately efficacious pharmacologic pain treatments available, often with limiting side effects and contraindications. Further compounding this is the limited understanding of the aetiology of pain in OA.

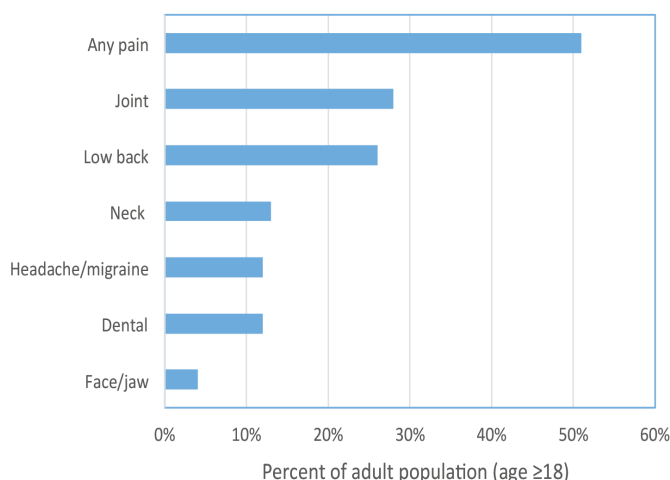
One barrier to understanding the genesis of pain in OA is the so-called “structure-symptom discordance”, which reflects the observation that some individuals have radiographic changes with minimal symptoms, while others have more significant pain with only minimal (if any) structural pathology noted on radiograph. OA is typically defined in epidemiologic studies on the basis of radiographic assessments, with prototypical findings of osteophytes with joint-space narrowing characterised as *radiographic OA*, while its combination with symptoms (*i.e.*, pain, aching, stiffness) in the same joint attributable to OA is considered to be *symptomatic OA*. Such nomenclature highlights the recognised discordance between structure and symptoms noted in OA. This has contributed to the ambiguity of the importance of structural contributions of OA pathology to the pain experience. While there have been reports of weak correlations between radiographic severity of OA and pain, the discordance diminishes with more severe stages of disease. Nonetheless, in a systematic review, 15–76% of those with knee pain

Competing interests: none declared.

had radiographic OA, and 15–81% of those with radiographic OA had knee pain (8). A number of factors influence the widely varying estimates, including imaging of only the tibiofemoral joint rather than also including the patellofemoral joint, which can certainly contribute to symptoms; acquisition of radiographs of both components of the knee joint improves the degree of concordance. Differences in the way in which pain symptoms are ascertained and the nature of the study sample (*e.g.*, age, sex distribution) also affect the prevalence of these findings and the degree of concordance. It has also been increasingly recognised that radiographs are relatively insensitive to numerous pathologic changes occurring in OA that are better visualised on MRI, with the recognition that OA is a disease of the whole joint. As proof-of-concept that something within the knee must be contributing to symptoms, one can look to the example of joint replacement, which is highly effective in improving symptoms for the majority of individuals, suggesting that the removed structure must have been contributing to pain. Another example is that of a clinical trial of intra-articular lidocaine injection which decreased knee pain compared with placebo injection (9).

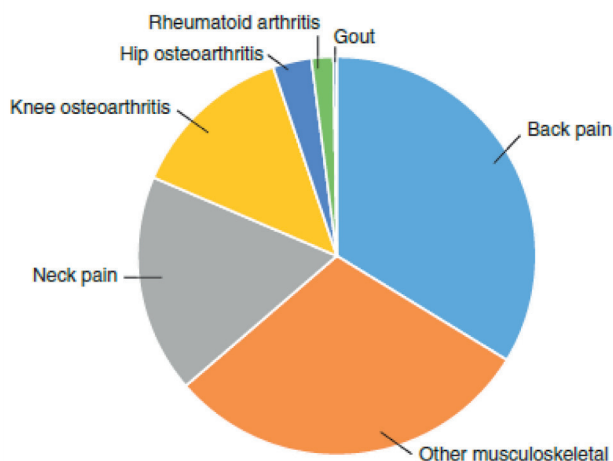
An often overlooked issue in interpreting studies of pain in OA is the fact that pain is a subjective experience, influenced by many factors that differ between individuals, including psychological factors (*e.g.*, catastrophising, coping skills), genetics, sociocultural environment, etc. Without adequately controlling for such factors, the structure-symptom relationship remains confounded, preventing one from obtaining valid insights into its true nature. A challenge, of course, is that not all factors are necessarily measured or even understood to enable comprehensive control of these extraneous factors to ‘unmask’ the true contribution of structural pathology to the experience of pain in OA. Through use of a within-person knee-matched design in which all of those between-person differences are inherently controlled for, a strong relationship between radiographic stage

Fig. 1.



Source: NHIS 2007
http://www.cdc.gov/nchs/data/series/sr_10/SR_10_240.pdf
 Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2007. Vital and Health Statistics, Series 10, Number 240, May 2009. DHHS publication no. (PHS) 2009-1568.

Fig. 2. Relative Prevalence of Common Musculoskeletal Conditions



Source: Global Burden of Disease 2010
 March L, Smith EUR, Hoy DG, Cross MJ, Sanchez-Riera L, Blyth F, Buchbinder R, Vos T, Woolf AD: Burden of disability due to musculoskeletal (MSK) disorders. *Best Practice & Research Clinical Rheumatology*. 2014; 28: 353-366.

and pain severity can be demonstrated (Fig. 3) (10).

While these examples support joint pathology as contributing to pain, radiographic studies and response to intra-articular therapy or joint replacement do not provide insights into what particular articular structures may be contributing to pain. The subchondral bone, periosteum, ligaments, periarticular muscle, outer third of the meniscus, synovium, and joint capsule are richly innervated and the likely sources of nociception in OA, particularly early in the course of disease. In an arthros-

copy study, an awake, unanesthetised evaluation of the knee joint identified the synovium, joint capsule, infrapatellar fat pad, and outer layers of the meniscus as being painful, while cartilage, which is aneural in healthy joints, was not painful (bone was not probed as it is known to be painful) (11). However, as OA progresses, neurovascular invasion may disrupt the osteochondral junction (12), accompanied by growth of sensory nerves and increased expression of nerve growth factor (NGF), which can facilitate sensitisation, another pertinent mechanism for pain in

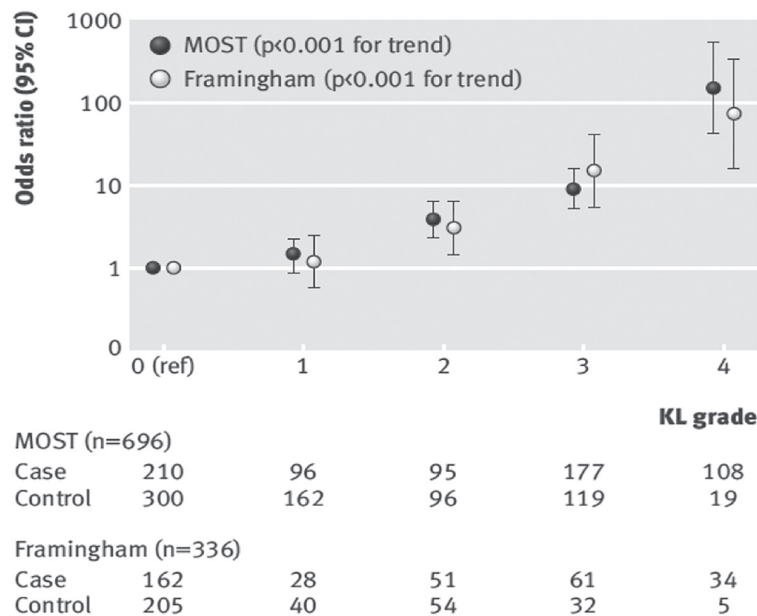


Fig. 3. Associations of frequent knee pain with Kellgren and Lawrence (KL) grade among people with two knees discordant for frequent knee pain status. Number of case knees (*i.e.*, with knee pain) and control knees (*i.e.*, without knee pain) are shown beneath the graph for each KL grade. Note the y-axis is logarithmically scaled.

Reference: Neogi T, et al. *BMJ* 2009;339:b2844 doi:10.1136/bmj.b2844.

OA, as discussed by Arendt-Nielsen in this issue (13).

Further insights into structural pathologic contributions to OA pain can be gleaned from MRI studies. A number of MRI studies have highlighted the importance of subchondral bone, particularly bone marrow lesions (BMLs) and synovitis/effusion as contributors to pain in OA (14-16). Of note, BMLs and synovitis/effusion have been associated not only with pain presence or severity, but also with pain fluctuation (17). Two recent clinical trials, one using IV zoledronic acid and the other using a patellofemoral knee brace, demonstrated reduction in pain along with reduction in BML volume, with the patellofemoral knee brace trial showing an effect on patellofemoral BMLs without affecting tibiofemoral BMLs (18, 19), supporting the targeting of this particular pathology to achieve symptom benefit. Synovitis is another attractive treatment target, with intra-articular corticosteroid injection commonly used, providing relatively short-term symptom relief for the most part (20). However, a recent trial did not demonstrate a longer term (2-year period) benefit despite enrolling subjects with evidence of synovitis/effusion by ultrasound; it is possible that

an adequate dose was not used and that transient shorter-term benefits were missed (21). While menisci are innervated and are potential contributors to pain in OA, meniscal lesions are common in OA and their contributions to symptoms is controversial. In a large epidemiologic study, meniscal tears were equally as prevalent among those with knee pain as those without (22). It should also be noted that interpretation of MRI abnormalities in knees of older adults can be challenging as 89% without any radiographic evidence of knee OA have at least one MRI feature of OA, with similar prevalence in both painful and pain-free knees (23).

Thus, while there is strong, supportive evidence for an important role of structural pathology to the contribution of knee pain in OA, there are also other factors that importantly influence symptoms. More recently, the importance of neurobiological mechanisms has been recognised, particularly of sensitisation, as discussed in greater detail by Arendt-Nielsen in this issue (13). Of relevance to understanding the structural pathologic contributions to pain, insights into the relation of OA pathology to sensitisation has been reported. While pain sensitisation is strongly as-

sociated with pain severity in knee OA, sensitisation itself is not associated with radiographic OA severity (24, 25). On the other hand, synovitis and effusion, but not BMLs, were associated with worsening or development of sensitisation (26).

Conclusions

In summary, the contribution of structural joint pathology to the pain experience in OA remains incompletely understood, but the advent of MRI and appropriate approaches to study designs have begun to shed light onto specific pathologic features that likely play an important role in the etiology of pain in OA. Gaining further insights into these relationships will provide much-needed guidance for pertinent treatment targets in knee OA. At the same time, clinicians and investigators must bear in mind that factors beyond structural pathology also contribute to the pain experience that should ideally be addressed, including psychological factors. Other factors that may offer new avenues for treatment targets, such as pain sensitisation and the overall efficiency of CNS pain modulating mechanisms, merit further evaluation, particularly to understand whether structural pathology contributes to sensitisation. A better understanding of the mechanisms by which structural pathology contributes to pain in OA is urgently needed to enable pursuit of novel treatment targets to help the millions of people worldwide who are burdened by pain from OA.

References

1. LIM SS, VOS T, FLAXMAN AD *et al.*: A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2224-60.
2. Prevalence and impact of chronic joint symptoms – seven states, 1996. *MMWR - Morbidity & Mortality Weekly Report* 1998; 47: 345-51.
3. DUNLOP DD, MANHEIM LM, SONG J, CHANG RW: Arthritis prevalence and activity limitations in older adults. *Arthritis Rheum* 2001; 44: 212-21.
4. LAWRENCE RC, FELSON DT, HELMICK CG *et al.*: Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008; 58: 26-35.

5. LAWRENCE RC, HELMICK CG, ARNETT FC *et al.*: Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; 41: 778-99.
6. Prevalence of disabilities and associated health conditions among adults -- United States 1999. [erratum: MMWR Morb Mortal Wkly Rep 2001 Mar 2; 50(8): 149.]. *MMWR - Morbidity & Mortality Weekly Report* 2001;50:120-25.
7. GUCCIONE AA, FELSON DT, ANDERSON JJ *et al.*: The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994; 84: 351-8.
8. BEDSON J, CROFT PR: The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord* 2008; 9: 116.
9. CREAMER P, HUNT M, DIEPPE P: Pain mechanisms in osteoarthritis of the knee: effect of intraarticular anesthetic. *J Rheumatol* 1996; 23: 1031-6.
10. NEOGI T, FELSON D, NIU J *et al.*: Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ* 2009; 339: b2844.
11. DYE SF, VAUPEL GL, DYE CC: Conscious neurosensory mapping of the internal structures of the human knee without intraarticular anesthesia. *Am J Sports Med* 1998; 26: 773-7.
12. WALSH DA, MCWILLIAMS DF, TURLEY MJ *et al.*: Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology (Oxford)* 2010; 49: 1852-61.
13. ARENDT-NIELSEN: Pain sensitization in osteoarthritis. *Clin Exp Rheumatol* 2017; 35 (Suppl. 107): S68-74.
14. HUNTER DJ, GUERMAZI A, ROEMER F, ZHANG Y, NEOGI T: Structural correlates of pain in joints with osteoarthritis. *Osteoarthritis Cartilage* 2013; 21: 1170-8.
15. YUSUF E, KORTEKAAS MC, WATT I, HUIZINGA TW, KLOPPENBURG M: Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis* 2011; 70: 60-7.
16. HUNTER DJ, ZHANG W, CONAGHAN PG *et al.*: Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. *Osteoarthritis Cartilage* 2011; 19: 557-88.
17. ZHANG Y, NEVITT M, NIU J *et al.*: Fluctuation of knee pain and changes in bone marrow lesions, effusions and synovitis on MRI: The Most Study. *Arthritis Rheum* 2011; 63: 691-99.
18. LASLETT LL, DORE DA, QUINN SJ *et al.*: Zoledronic acid reduces bone marrow lesions and knee pain over one year. *Ann Rheum Dis* 2011;70 (Suppl. 3):138.
19. CALLAGHAN MJ, PARKES MJ, HUTCHINSON CE *et al.*: A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. *Ann Rheum Dis* 2015; 74: 1164-70.
20. ARROLL B, GOODYEAR-SMITH F: Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ* 2004; 328: 869.
21. MCALINDON TE, LAVALLEY MP, HARVEY WF *et al.*: Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. *JAMA* 2017; 317: 1967-75.
22. ENGLUND M, GUERMAZI A, GALE D *et al.*: Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008; 359: 1108-15.
23. GUERMAZI A, NIU J, HAYASHI D *et al.*: Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). *BMJ* 2012; 345: e5339.
24. FINAN PH, BUENAVAR LF, BOUNDS SC *et al.*: Discordance between pain and radiographic severity in knee osteoarthritis: Findings from quantitative sensory testing of central sensitization. *Arthritis Rheum* 2013; 65: 363-72.
25. NEOGI T, FREY-LAW L, SCHOLZ J *et al.*: Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? *Ann Rheum Dis* 2015; 74: 682-8.
26. NEOGI T, GUERMAZI A, ROEMER F *et al.*: Association of joint inflammation with pain sensitization in knee osteoarthritis: the multicenter osteoarthritis study. *Arthritis Rheumatol* 2016; 68: 654-61.