

Sources of pain in osteoarthritis: implications for therapy

Osteoarthritis is the leading musculoskeletal cause of disability in western society. Despite this, it is still difficult to gain a precise definition of what osteoarthritis actually is. It is well known that there is a modest correlation between x-ray changes and pain. However, for knee joint structure there is largely consistent evidence that bone marrow lesions, synovitis/effusions and cartilage defects are associated with knee pain and cartilage loss. In addition, muscle strength and obesity predict pain even in the absence of structural knee pathology. Finally, the pain system itself is involved with both pain processing and genetic factors implicated in recent studies. These improvements in basic science have greatly enhanced our understanding that osteoarthritis is an umbrella term for a number of pathways leading to very similar pain and structural outcomes; these outcomes are leading to lesion-specific therapies, which indicate the importance of trying to pinpoint causes of pain in the individual.

KEYWORDS: epidemiology ■ osteoarthritis ■ pain ■ therapy

Graeme Jones

Menzies Research Institute, University of Tasmania, Private bag 23, Hobart, Tasmania 7000, Australia
g.jones@utas.edu.au



Medscape: Continuing Medical Education Online

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medscape, LLC and Future Medicine Ltd. Medscape, LLC is accredited by the ACCME to provide continuing medical education for physicians.

Medscape, LLC designates this Journal-based CME activity for a maximum of **1 AMA PRA Category 1 Credit(s)™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test with a 70% minimum passing score and complete the evaluation at www.medscape.org/journal/ijcr; (4) view/print certificate.

Release date: 26 June 2013; Expiration date: 26 June 2014

Learning objectives

Upon completion of this activity, participants should be able to:

- Assess the association between radiologic findings and pain in osteoarthritis (OA)
- Analyze the relationship between cartilage defects in the knee and pain among patients with OA
- Distinguish other variables associated with knee pain among patients with OA
- Evaluate variables associated with pain in other anatomic locations of OA

Future
Medicine  part of 

Financial & competing interests disclosure

CME Author

Charles P Vega, MD, Associate Professor and Residency Director, Department of Family Medicine, University of California, Irvine, CA, USA

Disclosure: Charles P Vega, MD, has disclosed no relevant financial relationships.

Authors and Disclosures

Graeme Jones, MD, Professor of Rheumatology and Epidemiology; Head of the Musculoskeletal Unit, Menzies Research Institute, University of Tasmania, Hobart, Tasmania, Australia

Disclosure: Graeme Jones, MD, has disclosed no relevant financial relationships.

Editor

Elisa Manzotti, Publisher, Future Science Group, London, UK

Disclosure: Elisa Manzotti has disclosed no relevant financial relationships.

Osteoarthritis as a public health problem

Osteoarthritis (OA) is the most common form of arthritis and its prevalence is increasing markedly owing to an aging population. It is characterized by a gradual loss of articular cartilage and changes to other joint structures, eventually leading to total joint replacement. OA is the most common joint disorder worldwide, and in western populations, it is one of the most frequent causes of pain, loss of function and disability in adults [1]. It is pain that drives the patient to seek help and it is pain that interferes with quality of life; pain is very common and explains up to 30% of the variance in quality-of-life scores in those aged 50–80 years old [2].

The aim of this review is to update recent research on how to define OA, review the literature on factors associated with pain and discuss the implications of these findings for therapy. This review will focus on the knee but will also include other joints and will comprehensively discuss factors that have been independently associated with pain. Literature was identified on Medline using the search terms: pain, OA, human and/or clinical/epidemiological.

Definitions of OA vary using clinical features, radiographs or MRI

Currently, the definition of OA utilizes a combination of symptoms and radiographic criteria [3]. While this definition is useful for epidemiologic studies, a number of questions remain unanswered. Standard radiographs have been criticized as insensitive due to their 2D nature, measurement error and semiquantitative assessment [4]. At best, most x-ray-grading scales at best provide a broad-brush assessment of the joint, mainly with assessment of osteophytes and joint space narrowing, which most probably provides a limited view of the disease process. Furthermore, radiographic OA only has a weak correlation with symptoms (see sections

Knee and Radiographs), leading most people to assume that there is a disconnection between symptoms and structural change. MRI provides a high-powered view of the structures within the knee. It can directly visualize knee structures, including cartilage volume, cartilage defects, cartilage biochemistry, meniscal pathology, bone marrow lesions (BMLs) and subchondral bone size [5]. Recently, Hunter *et al.* conducted a detector with lepton, photon and hadron identification (DELPHI) experiment for defining knee OA on MRI scanning [5]. The diagnostic performance was greatest for osteophytes, cartilage loss, BMLs and for meniscus tear in any region. This resulted in good specificity but less optimal sensitivity, probably owing to detection of disease earlier on MRI. It is clear that many of these abnormalities are very common in asymptomatic elderly subjects [6], but the literature is maturing in terms of their association (or lack thereof) with pain.

■ Knee

TABLE 1 summarizes factors that have been associated with OA of the knee. FIGURE 1 shows that many of these factors can occur in the same subject indicating that they commonly coexist, which can make sorting out associations with pain difficult in the individual.

Radiographs

There have been many studies of this issue [7]. The proportion of those with knee pain found to have radiographic OA ranged from 15 to 76%, while in those with radiographic knee OA the proportion with pain ranged from 15 to 81%, indicating much discordance between pain and radiographic knee OA. Considerable variation occurred with x-ray view, pain definition, OA grading and demographic factors [7]. Overall, there is a modest but significant correlation between degree of radiographic change and knee pain, which is most consistent for osteophytes [7].

However, it remains uncertain whether either of the key radiographic changes (joint space narrowing or osteophytes) are causally related to knee pain. Indeed, a study from the authors of this reviews' group reported a significant association between osteophytes and pain, but this disappeared after adjustment for a number of factors assessed on MRI scanning, muscle strength and obesity [8], suggesting that osteophytes may be a reflection of the disease process, but not a key player. It is also unclear whether x-ray abnormalities help with choosing therapy.

MRI features

In individuals with unilateral knee pain, MRI (cartilage defects and synovitis/effusion) and radiographic features were associated with knee pain, confirming that structural abnormalities in the knee have an important role in the etiology of pain. However, in this study, no single MRI or radiographic finding performed well in discriminating between painful and nonpainful knees, indicating that MRI and radiography probably make smaller independent contributions, which this study may not have been large enough to disentangle [9].

Bone marrow lesions

There is strong and increasing human evidence that bone plays an important role in the pathogenesis of OA [10]; BMLs have been recognized as a key feature of knee OA [11,12]. A number of studies have linked BMLs with knee pain [8,11–15], although other smaller studies have failed to demonstrate such a relationship [16,17]. In pain-free populations, incident BMLs [14] and increases in BMLs [13] have been shown to be associated with the development of knee pain. However, other studies in mostly OA subjects have reported no association between changes in BMLs and Western Ontario and McMaster Universities OA (WOMAC) index pain scores after 2 years [16], or changes in WOMAC scores [17]. There are now two papers that show a significant correlation between change in BMLs and change in pain both in unselected community living [12] and OA populations [18]. The association was most obvious in those without radiographic change [12]; however, a decrease in BML score was associated with a decrease in pain in both studies, suggesting a potential target for therapy. Indeed, a report of a proof-of-principle trial, carried out only in those with BMLs, demonstrated that zoledronic acid (a potent bone-acting bisphosphonate) could decrease both pain and BML size compared with placebo over 6 months [19]. Another

Table 1. Factors implicated in knee pain.

Factor	Independently associated with pain	Ref.
Obesity	Yes	[8]
Muscle strength	Yes	[8]
Bone marrow lesions	Yes	[8,11–15,19]
Tibial bone size	No	[8]
Subchondral bone mass	No	[JONES G, UNPUBLISHED DATA]
Osteophyte	Yes [†]	[7,8]
Meniscal tear	Yes (if macerated or posterior horn)	[25,28,29]
Meniscal extrusion	No	[JONES G, UNPUBLISHED DATA]
Cartilage defects	Yes	[8,23–26]
Effusion	Yes	[15]
Synovitis	Yes	[30]

[†]Not independent of other factors in [8].

trial of chondroitin sulphate in subjects who had knee OA (but were not selected based on BMLs) showed a decrease in BML size over 12 months but no change in pain [20]. These early studies are encouraging and suggest that targeting the bone may require shorter studies compared with radiographic trials as significant changes were seen in 6 months compared with 3 years for trials with a x-ray outcome.

Cartilage defects

Cartilage defects are very common, being present in high proportions of subjects in many studies [10]. They become more frequent with increasing age, female sex and BMI [10]. Cartilage is aneural; therefore, defects in cartilage should not be associated with pain. Despite this, there is consistent evidence that cartilage defects are linked to pain, and this is largely independent of other structural factors. Women with full-thickness knee cartilage defects accompanied by adjacent subchondral cortical bone defects are more likely to have knee pain in the presence of radiographic OA [21]. Furthermore, knee cartilage defects were independently and significantly associated with knee pain in a dose–response fashion in a younger cohort [22]. In addition, in a sample of 500 randomly selected older men and women, prevalence and severity of knee pain were significantly associated with medial tibial cartilage defects [8]. Interestingly, there was a dose–response association between knee pain and the number of sites having grade 3 or 4 cartilage defects, with 100% of subjects having knee pain if all compartments of the knee had

these defects. Additionally, in 143 subjects with primary knee OA, knee cartilage defects were weakly but significantly associated with pain severity [23]. These defects were independent of BMLs, but synovitis/effusion was not assessed in most of these studies. Finally, in 50 subjects with knee OA, knee cartilage defects were also significantly associated with the WOMAC pain and function scores [24].

Cartilage defects strongly correlate with BMLs, suggesting that BMLs and cartilage defects are closely related, but both have independent associations with pain. The association between knee pain and cartilage defects was independent of BMI, muscle strength, radiographic OA and BMLs in one study [8]. A more recent study suggested that the association was also independent of large osteophytes, marked synovitis and macerated meniscal tears, suggesting damaged articular cartilage may independently lead to knee pain [25]. This may be mediated by substance P nociceptive fibers [26] or superinduction of COX2 and prostaglandins [27]. This may also reflect the phenomenon of neoangiogenesis and vascular invasion of calcified cartilage and the tide mark breaking with consequent perivascular nerve fiber invasion of the deep zone of hyaline cartilage [10].

Meniscal pathology

The association between meniscal pathology and pain remains controversial and may reflect site-specific associations. Any meniscal damage was

associated with knee pain but not after adjustment for radiographic OA [28]. In a study from the authors' institution, meniscal tear at the lateral posterior and anterior horns, but not at other sites, was significantly associated with WOMAC pain, stiffness and function scores [29]. In another study, macerated tears were associated with pain [25].

Inflammation

Traditionally, OA was thought to be a noninflammatory condition. It is now clear that this is not the case, although inflammation tends to be lower grade and joint based (rather than systemic) when compared with rheumatoid arthritis. It also seems difficult to diagnose OA if there is only synovitis present, thus one would prefer to see a BML, cartilage damage or meniscal damage in addition to synovitis or consider other causes. The evidence is not totally consistent but strongly links local inflammation (measured as synovitis and/or effusions) with pain [15]. Furthermore, changes in synovitis (but not effusion severity) are associated with fluctuations in knee pain in patients with knee OA in two studies, suggesting that synovitis may be the key factor and effusion occurs as a consequence of synovitis [30]. Intriguingly, C-reactive protein levels in serum are also predictive of knee pain development over 5 years, and this association was independent of all measured knee structural abnormalities in that study [31]. The author's group did not measure synovitis; however, the association changed little after adjustment for effusion, suggesting that both local and systemic inflammation are risk factors for knee pain. In terms of therapy, this opens up a number of options. Corticosteroid injections are effective for pain in knee OA but seem to be most effective for effusion [32]; thus, it would seem logical to preferentially give them to those with effusions. There are some early case series data suggesting that TNF blockade will also work in those with effusions [33], but this needs confirmation in a randomized trial. NSAIDs help pain in OA; however, there are limited data on who they may work best in [34].

Other knee structures

There is generally consistent evidence that knee bone size, subchondral bone density, meniscal extrusion and cartilage volume are not associated with pain [8, JONES G *ET AL.*, UNPUBLISHED DATA].

Obesity

Obesity is a very strong independent correlate of knee pain that is consistently associated with OA in many studies [8,23,35]. BMI is most strongly associated with diffuse knee pain [36] and, again,

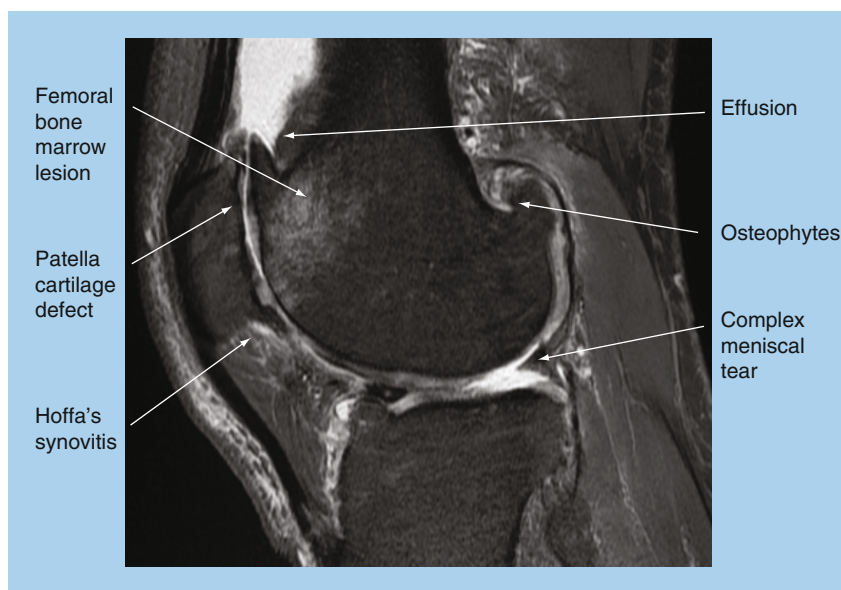


Figure 1. MRI of the knee showing a large femoral bone marrow lesion, patella cartilage defects, Hoffa's synovitis, a posterior horn meniscal tear, effusion and large osteophytes (all of which have been independently associated with pain).

this association is independent of structural change in the knee. In the NHANES study, the age- and BMI-adjusted prevalence of knee pain increased by approximately 65% from 1974 to 1994 among non-Hispanic white and Mexican-American men and women and among African-American women [37], while in the FOA study, the age- and BMI-adjusted prevalence of knee pain and symptomatic knee OA approximately doubled in women and tripled in men over 20 years [37]. BMI appeared to be responsible for 10–25% of this increase based on modeling.

There is level one evidence that weight loss improves knee symptoms [34,38], although, interestingly, weight gain is more strongly associated with worsening pain than weight loss being associated with improvements in pain, implying limited reversibility [39]. Nevertheless, in the overweight patient with limited structural pathology weight loss should be the main objective.

Weak muscles

Similar to obesity, weak muscles, especially quadriceps strength, are independently associated with pain both in cross-sectional [8] and longitudinal [40] studies. In subjects from the OA Initiative, knees with frequent pain demonstrate lower maximal cross-sectional areas and force of the quadriceps (but not of other thigh muscles) compared with contralateral knees without knee pain with the same radiographic stage [41]. There is level one evidence that both strengthening and aerobic exercises help pain in knee and hip OA [34]. Whether these therapies work better in those with weaker muscles is unknown.

Central factors & genetics

It is clear that pain in OA is also mediated by a number of central factors but it is not clear if these factors are specific to OA. Depression is consistently linked with pain experience in rheumatic diseases [42]. In the OA Initiative, depression had a small but significant effect on knee pain prospectively [43]. Catastrophization (the tendency to view or present a situation as considerably worse than it actually is) is associated with pain severity in most rheumatic diseases including OA [42]. Indeed, the tendency to catastrophize (rather than disease severity) appears to explain the well-known sex differences in OA pain [44]. Acceptance and self efficacy also appear to correlate with pain [45]. Finally, a positive attitude also appears to influence the participation in daily walking [46].

Knee pain has a strong heritable component [47]. Recently, there have been studies implicating

specific genes. These include *TRPV1*, *COMT* and *PCSK6*. *TRPV1* primarily has a role in afferent sensory neuron function and has been well demonstrated in both discovery and replication cohorts as having an association with pain (but not with radiographic OA) [48]. *COMT* is involved in central pain processing and has been linked in a single association study with hip OA in women. However, the data from this cohort on knee and hand were not published and it has not been replicated elsewhere, suggesting that this may be a false-positive result [49]. It has led to calls for OA of the knee to be considered a central pain problem, but this seems premature based on the evidence. Central changes occur on functional MRI scans in those with chronic pain [50]; however, this is not specific to those with OA, being seen in many other patients with chronic pain. The last study on *PACE4* again used a discovery and replication cohort and suggests that a variant in *PCSK6* is strongly associated with protection against pain in knee OA [51].

There are limited data regarding therapy, but there are two trials suggesting that duloxetine (a combination antidepressant) has a modest, but significant, effect on pain in OA of the knee [52]. It is not clear whether this reflects treatment of depression, fibromyalgia or other mechanisms of pain.

Weather

The association between weather and symptoms was thought to be a medical myth, but there are a number of studies in this area. Perhaps the best designed study was from McAlindon and colleagues [53]. The study included 200 participants with knee OA participating in a clinical trial with matched (but independently collected) meteorological data. There were consistent associations between pressure change and ambient temperature with pain severity and suggestive data for dew point (which reflects relative humidity at a given temperature).

■ Hand

There is limited literature for the hand and most studies are cross-sectional in design. Grip strength is associated with pain in a population-based family sample [54]. There are also data in this sample showing a modest correlation between radiographic change and pain with a correlation of 0.26, which appears greater compared with the knee studies. There is also a specific association between isolated thumb OA and thumb pain [55]. In a systematic review, key

factors associated with hand pain severity were age, impact, frustration, patient expectation of a long disease time course and self-reported diagnosis of the cause of the hand problem [56]. Recently, there has been literature indicating that a number of MRI features are associated with joint tenderness in a clinic population. These include MRI-defined moderate/severe synovitis, BMLs, erosions and attrition but not osteophytes (odds ratio [OR]: 1.4; $p = 0.10$) [57]. Interestingly, no significant associations were found with questionnaire assessments of pain or function, possibly owing to all patients being symptomatic. While it is desirable to confirm these findings in a less selected population, they do suggest a commonality to pathological processes and associations with the knee. Some recent trial data with adalimumab in erosive hand OA [58]. This demonstrated no overall effect, but a *post hoc* analysis suggested that this agent was effective for both symptoms and disease progression in those with soft-tissue swelling. This suggests adalimumab works where there is significant local inflammation. Such a hypothesis needs to be tested in a prospective design, but would be consistent with the rheumatoid arthritis literature where adalimumab works primarily on synovitis. Such a trial is underway in Australia [JONES G, PERS. COMM.], while a trial of hydroxychloroquine is underway in the UK [CONAGHAN P, PERS. COMM.].

■ Hip

When compared with the knee, data for the hip are much more limited. This contrasts with the osteophyte associations reported for the knee as a minimum joint space width of ≤ 2.0 mm was the radiographic criterion having the closest association with self-reported hip pain. Interestingly, composite OA scores emphasizing the formation of cysts, osteophytes and subchondral sclerosis added little to joint space width [59]. Birrell *et al.* also reported a strong association of pain with severe hip OA (OR: 17.4; 95% CI: 3.0–102), but a weaker and nonsignificant association with mild/moderate OA (OR: 1.4; 95% CI: 0.4–4.7) [60]. In a younger sample, independent predictors of hip pain onset were cumulative exposure to sitting for prolonged periods, lifting weights >50 lb (23 kg) and walking as a leisure activity [61]. The population-attributable risk associated with each of these activities was 21, 13 and 16%, respectively, suggesting that certain activity patterns can explain up to 50% of the pain. Cam deformity of the hip is considered to be a pre-osteoarthritic malformation causing premature

hip joint degeneration. However, in a large study, there was no association between cam deformity and hip pain, casting doubt on the clinical significance of this abnormality [62]. Finally, the authors found an association between hip joint space narrowing and knee pain that was independent of all other factors measured in and around the knee, indicating that referred pain from the hip is also a common source of knee pain [8].

■ Foot

Again, this is an area where there are limited data [63–65]. The evidence indicates: a strong association between increased BMI and nonspecific foot pain; and a strong association between increased BMI and chronic plantar heel pain. In particular, fat mass (but not lean mass) is a strong correlate of diffuse foot pain while the severity of hallux valgus is associated with foot pain and quality of life in a nonathletic population. The evidence is inconclusive regarding the relationship between BMI and specific disorders of the foot (hallux valgus, tendonitis, OA and flat foot).

■ Back

Back pain is multifactorial in nature and it is beyond the scope of this review to cover this area in depth. It is also difficult to determine what represents OA of the spine. The same general comments appear to relate to the association between radiographic change and pain with weak or no association reported in most studies [66]. It is relevant to mention Modic change as the appearance of this appears similar to BMLs at other sites. There is consistent evidence linking these changes with pain; however, the strength of the association varies with ORs ranging from 2.0 to 19.9 [67]. Interestingly, there is a study in the bone literature demonstrating that zoledronate improved back pain in a clinical trial, and this was independent of changes in bone mass or fracture risk. The mechanism is uncertain but it is reasonable to hypothesize that it may be helping Modic change [68].

Conclusion & future perspective

Notwithstanding the above definitions it would seem more logical to regard knee (and perhaps other forms of) OA as an umbrella term for a number of different pathological processes that result in cartilage loss. Symptomatic OA would be where the individual has a structural abnormality and pain. It would seem most appropriate to remove x-ray from these diagnostic criteria

given that joint space narrowing merely reflects the final common pathways of not only cartilage loss but also cartilage defects, meniscal tears and extrusion, while osteophytes are of uncertain relevance to the pathophysiology (either pain or cartilage loss). This would allow the development of pathophysiology-specific therapies,

such as bone agents for BMLs, weight loss for the obese or exercise for the weak, rather than assuming that the same treatment works more or less the same for all patients with OA. Data are at too early a stage to comment with any certainty; however, the hand and hip data suggest pathology may well be similar at other sites.

Executive summary

- There is a weak correlation between radiographic changes and pain in osteoarthritis.
- MRI allows a more in-depth view of the joint and has identified structural factors that are important for pain, cartilage loss and/or both.
- Factors outside the joint are also important for pain.
- Management should be tailored to the cause of pain in an individual.

References

Papers of special note have been highlighted as:
▪ of interest

- 1 Felson DT. Clinical practice. Osteoarthritis of the knee. *N. Engl. J. Med.* 354, 841–848 (2006).
- 2 Laslett LL, Quinn S, Winzenberg T, Sanderson K, Cicuttini FM, Jones G. A prospective study of the impact of musculoskeletal pain and radiographic osteoarthritis on health related quality of life in community dwelling older people. *BMC Musculoskelet. Disord.* 13, 168 (2012).
- **Shows that pain at all sites (apart from the hip) is associated with reduced quality of life.**
- 3 Sharma L, Kapoor D, Issa S. Epidemiology of osteoarthritis: an update. *Curr. Opin. Rheumatol.* 18, 147–156 (2006).
- 4 Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. *Osteoarthritis Cartilage* 12, 169–174 (2004).
- 5 Hunter DJ, Arden N, Conaghan PG *et al.*; OARSI OA Imaging Working Group. Definition of osteoarthritis on MRI: results of a Delphi exercise. *Osteoarthritis Cartilage* 19, 963–969 (2011).
- 6 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* 345, e5339 (2012).
- 7 Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet. Disord.* 9, 116 (2008).
- 8 Zhai G, Blizzard L, Srikanth V *et al.* Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. *Arthritis Rheum.* 55, 264–271 (2006).
- **Shows which structural factors correlate with knee pain in a large population-based sample.**
- 9 Javaid MK, Kiran A, Guermazi A *et al.* Individual magnetic resonance imaging and radiographic features of knee osteoarthritis in subjects with unilateral knee pain: the health, aging, and body composition study. *Arthritis Rheum.* 64, 3246–3255 (2012).
- 10 Ding C, Cicuttini F, Jones G. Tibial subchondral bone size and knee cartilage defects: relevance to knee osteoarthritis. *Osteoarthritis Cartilage* 15, 479–486 (2007).
- 11 Felson DT, Chaisson CE, Hill CL *et al.* The association of bone marrow lesions with pain in knee osteoarthritis. *Ann. Intern. Med.* 134, 541–549 (2001).
- 12 Dore D, Quinn S, Ding C *et al.* Natural history and clinical significance of MRI-detected bone marrow lesions at the knee: a prospective study in community dwelling older adults. *Arthritis Res. Ther.* 12, R223 (2010).
- 13 Felson DT, Niu J, Guermazi A *et al.* Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. *Arthritis Rheum.* 56, 2986–2992 (2007).
- 14 Davies-Tuck ML, Wluka AE, Wang Y, English DR, Giles GG, Cicuttini F. The natural history of bone marrow lesions in community-based adults with no clinical knee osteoarthritis. *Ann. Rheum. Dis.* 68, 904–908 (2009).
- 15 Lo GH, McAlindon TE, Niu J *et al.* Bone marrow lesions and joint effusion are strongly and independently associated with weight-bearing pain in knee osteoarthritis: data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 17, 1562–1569 (2009).
- 16 Kornaat PR, Kloppenburg M, Sharma R *et al.* Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur. Radiol.* 17, 3073–3078 (2007).
- 17 Phan CM, Link TM, Blumenkrantz G *et al.* MR imaging findings in the follow-up of patients with different stages of knee osteoarthritis and the correlation with clinical symptoms. *Eur. Radiol.* 16, 608–618 (2006).
- 18 Zhang Y, Nevitt M, Niu J *et al.* Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis Rheum.* 63, 691–699 (2011).
- 19 Laslett LL, Doré D, Quinn S *et al.* Zoledronic acid reduces knee pain and bone marrow lesions over one year: a randomised controlled trial. *Ann. Rheum. Dis.* 71, 1322–1328 (2012).
- **Novel proof-of-principle trial suggesting that bone agents will be effective for bone marrow lesions.**
- 20 Wildi LM, Raynauld JP, Martel-Pelletier J *et al.* Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. *Ann. Rheum. Dis.* 70, 982–989 (2011).
- 21 Sowers MF, Hayes C, Jamadar D *et al.* Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and x-ray-defined knee osteoarthritis. *Osteoarthritis Cartilage* 11, 387–393 (2003).
- 22 Zhai G, Cicuttini F, Ding C, Scott F, Garner P, Jones G. Correlates of knee pain in younger subjects. *Clin. Rheumatol.* 26, 75–80 (2006).
- 23 Torres L, Dunlop DD, Peterfy C *et al.* The relationship between specific tissue lesions and pain severity in persons with knee

- osteoarthritis. *Osteoarthritis Cartilage* 14, 1033–1040 (2006).
- 24 Link TM, Steinbach LS, Ghosh S *et al.* Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 226, 373–381 (2003).
- 25 Sowers M, Karvonen-Gutierrez CA, Jacobson JA, Jiang Y, Yosef M. Associations of anatomical measures from MRI with radiographically defined knee osteoarthritis score, pain, and physical functioning. *J. Bone Joint Surg. Am.* 93, 241–251 (2011).
- 26 Fortier LA, Nixon AJ. Distributional changes in substance P nociceptive fiber patterns in naturally osteoarthritic articulations. *J. Rheumatol.* 24, 524–530 (1997).
- 27 Amin AR, Attur M, Patel RN *et al.* Superinduction of cyclooxygenase-2 activity in human osteoarthritis-affected cartilage. Influence of nitric oxide. *J. Clin. Invest.* 99, 1231–1237 (1997).
- 28 Englund M, Niu J, Guermazi A *et al.* Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness. *Arthritis Rheum.* 56, 4048–4054 (2007).
- 29 Ding C, Martel-Pelletier J, Pelletier J-P *et al.* Is meniscal tear an osteoarthritis risk factor? A cross-sectional study of associations between meniscal tear and knee structure, radiographic changes and symptoms in a largely non-osteoarthritic cohort. *J. Rheumatol.* 34, 776–784 (2007).
- 30 Hill CL, Hunter DJ, Niu J *et al.* Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Ann. Rheum. Dis.* 66, 1599–1603 (2007).
- 31 Stannus O, Jones G, Cicuttini F *et al.* Associations between serum levels of inflammatory markers and change in knee pain over 5 years in older adults: a prospective cohort study. *Ann. Rheum. Dis.* 72(4), 535–540 (2013).
- 32 Smith MD, Wetherall M, Darby T *et al.* A randomized placebo-controlled trial of arthroscopic lavage versus lavage plus intra-articular corticosteroids in the management of symptomatic osteoarthritis of the knee. *Rheumatology* 42, 1477–1485 (2003).
- 33 Maksymowych WP, Russell AS, Chiu P *et al.* Targeting tumour necrosis factor alleviates signs and symptoms of inflammatory osteoarthritis of the knee. *Arthritis Res. Ther.* 14, R206 (2012).
- 34 Zhang W, Nuki G, Moskowitz RW *et al.* OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 18, 476–499 (2010).
- **Informative review on therapy for knee and hip osteoarthritis (OA).**
- 35 Soni A, Kiran A, Hart DJ *et al.* Prevalence of reported knee pain over twelve years in a community-based cohort. *Arthritis Rheum.* 64, 1145–1152 (2012).
- 36 Thompson LR, Boudreau R, Newman AB *et al.* The association of osteoarthritis risk factors with localized, regional and diffuse knee pain. *Osteoarthritis Cartilage* 18, 1244–1249 (2010).
- 37 Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Ann. Intern. Med.* 155, 725–732 (2011).
- 38 Gudbergson H, Boesen M, Lohmander LS *et al.* Weight loss is effective for symptomatic relief in obese subjects with knee osteoarthritis independently of joint damage severity assessed by high-field MRI and radiography. *Osteoarthritis Cartilage* 20, 495–502 (2012).
- 39 Tanamas S, Wluka A, Berry P *et al.* Weight gain is associated with worsening of knee pain, stiffness, and function: a longitudinal study. *Arthritis Care Res.* 65, 34–43 (2012).
- 40 Amin S, Baker K, Niu J *et al.* Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis. *Arthritis Rheum.* 60, 189–198 (2009).
- 41 Sattler M, Dannhauer T, Hudelmaier M *et al.* Side differences of thigh muscle cross-sectional areas and maximal isometric muscle force in bilateral knees with the same radiographic disease stage, but unilateral frequent pain – data from the osteoarthritis initiative. *Osteoarthritis Cartilage* 20, 532–540 (2012).
- 42 Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. *Nat. Rev. Rheumatol.* 7, 216–224 (2011).
- 43 Riddle DL, Kong X, Fitzgerald GK. Psychological health impact on 2-year changes in pain and function in persons with knee pain: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 19, 1095–1101 (2011).
- 44 Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. *Pain* 87, 325–334 (2000).
- 45 Somers TJ, Keefe FJ, Godiwala N, Hoyler GH. Psychosocial factors and the pain experience of osteoarthritis patients: new findings and new directions. *Curr. Opin. Rheumatol.* 21, 501–506 (2009).
- **Excellent review on central factors and pain in OA.**
- 46 White DK, Keysor JJ, Neogi T *et al.* When it hurts, a positive attitude may help: association of positive affect with daily walking in knee osteoarthritis. Results from a multicenter longitudinal cohort study. *Arthritis Care Res.* 64, 1312–1319 (2012).
- 47 Zhai G, Jones G, Ding C, Scott F, Cicuttini F. The genetic contribution to muscle strength, knee pain, cartilage volume, bone size and radiographic osteoarthritis: a sibpair Study. *Arthritis Rheum.* 50, 805–810 (2004).
- 48 Valdes AM, De Wilde G, Doherty SA *et al.* The Ile585Val *TRPV1* variant is involved in risk of painful knee osteoarthritis. *Ann. Rheum. Dis.* 70, 1556–1561 (2011).
- **Demonstrates that a gene variant differentiates those with pain from those without pain.**
- 49 van Meurs JB, Uitterlinden AG, Stolk L *et al.* A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain. *Arthritis Rheum.* 60, 628–629 (2009).
- 50 Arendt-Nielsen L, Nie H, Laursen MB *et al.* Sensitization in patients with painful knee osteoarthritis. *Pain* 149, 573–581 (2010).
- 51 Malfait AM, Seymour AB, Gao F *et al.* A role for *PACE4* in osteoarthritis pain: evidence from human genetic association and null mutant phenotype. *Ann. Rheum. Dis.* 71, 1042–1048 (2012).
- 52 Hochberg MC, Wohlreich M, Gaynor P, Hanna S, Risser R. Clinically relevant outcomes based on analysis of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis. *J. Rheumatol.* 39, 352–358 (2012).
- **Demonstrates that antidepressants may work for OA pain.**
- 53 McAlindon T, Formica M, Schmid CH, Fletcher J. Changes in barometric pressure and ambient temperature influence osteoarthritis pain. *Am. J. Med.* 120, 429–434 (2007).
- 54 Jones G, Cooley H, Bellamy N. A cross-sectional study of the association between Heberden's nodes, radiographic osteoarthritis of the hands, grip strength, disability and pain. *Osteoarthritis Cartilage* 9, 606–611 (2001).
- 55 Marshall M, van der Windt D, Nicholls E, Myers H, Dziedzic K. Radiographic thumb osteoarthritis: frequency, patterns and associations with pain and clinical assessment findings in a community-dwelling

- population. *Rheumatology (Oxford)* 50, 735–739 (2011).
- 56 Nicholls EE, van der Windt DA, Jordan JL, Dziedzic KS, Thomas E. Factors associated with the severity and progression of self-reported hand pain and functional difficulty in community-dwelling older adults: a systematic review. *Musculoskelet. Care* 10, 51–62 (2012).
 - 57 Haugen IK, Bøyesen P, Slatkowsky-Christensen B, Sesseng S, van der Heijde D, Kvien TK. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann. Rheum. Dis.* 71, 899–904 (2012).
 - **First paper that discusses MRI features associated with hand tenderness.**
 - 58 Verbruggen G, Wittoek R, Vander Cruyssen B, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann. Rheum. Dis.* 71, 891–898 (2012).
 - **Proof-of-principle trial suggesting TNF blockade may prevent deterioration in hand OA.**
 - 59 Jacobsen S, Sonne-Holm S, Søballe K, Gebuhr P, Lund B. Radiographic case definitions and prevalence of osteoarthritis of the hip: a survey of 4151 subjects in the Osteoarthritis Substudy of the Copenhagen City Heart Study. *Acta Orthop. Scand.* 75, 713–720 (2004).
 - 60 Birrell F, Lunt M, Macfarlane G, Silman A. Association between pain in the hip region and radiographic changes of osteoarthritis: results from a population-based study. *Rheumatology (Oxford)* 44, 337–341 (2005).
 - 61 Pope DP, Hunt IM, Birrell FN, Silman AJ, Macfarlane GJ. Hip pain onset in relation to cumulative workplace and leisure time mechanical load: a population based case-control study. *Ann. Rheum. Dis.* 62, 322–326 (2003).
 - 62 Gosvig KK, Jacobsen S, Sonne-Holm S, Gebuhr P. The prevalence of cam-type deformity of the hip joint: a survey of 4151 subjects of the Copenhagen Osteoarthritis Study. *Acta Radiol.* 49, 436–441 (2008).
 - 63 Butterworth PA, Landorf KB, Smith SE, Menz HB. The association between body mass index and musculoskeletal foot disorders: a systematic review. *Obes. Rev.* 13, 630–642 (2012).
 - 64 Tanamas S, Wluka A, Berry P *et al.* The relationship between obesity and foot pain is related to fat mass and fat distribution but not muscle mass. *Arthritis Care Res.* 64, 262–268 (2012).
 - 65 Menz HB, Roddy E, Thomas E, Croft PR. Impact of hallux valgus severity on general and foot-specific health-related quality of life. *Arthritis Care Res.* 63, 396–404 (2011).
 - 66 Muraki S, Oka H, Akune T *et al.* Prevalence of radiographic lumbar spondylosis and its association with low back pain in elderly subjects of population-based cohorts: the ROAD study. *Ann. Rheum. Dis.* 68, 1401–1406 (2009).
 - 67 Jensen TS, Karppinen J, Sorensen JS, Niinimäki J, Leboeuf-Yde C. Vertebral endplate signal changes (Modic change): a systematic literature review of prevalence and association with non-specific low back pain. *Eur. Spine J.* 17, 1407–1422 (2008).
 - 68 Cauley JA, Black D, Boonen S *et al.* Once-yearly zoledronic acid and days of disability, bed rest, and back pain: randomized, controlled HORIZON Pivotal Fracture Trial. *J. Bone Miner. Res.* 26, 984–992 (2011).

Medscape EDUCATION Sources of pain in osteoarthritis: implications for therapy

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 70% passing score) and earn continuing medical education (CME) credit, please go to www.medscape.org/journal/ijcr. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the New Users: Free Registration link on the left hand side of the website to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the

accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to <http://www.ama-assn.org/ama/pub/category/2922.html>. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for **AMA PRA Category 1 Credits™**. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the AMA PRA CME credit certificate and present it to your national medical association for review.

Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are seeing a 70-year-old woman with previous diagnoses of osteoarthritis (OA) of the knees, hips, and hands. She has been experiencing more pain in general over the past 3 months and she wants to review her previous x-ray and MRI results with you. What can you tell her about the association between radiology studies and knee pain in OA?

- ☐ A Only osteophytes on knee radiographs are causally related to pain
- ☐ B Only joint space narrowing on knee radiographs are causally related to pain
- ☐ C X-ray abnormalities are not helpful in selecting treatment for OA
- ☐ D Synovitis on MRI reliably discriminates between painful and non-painful knees in cases of OA

2. The patient's MRI of the knee demonstrates cartilage defects. Which of the following statements regarding these changes is most accurate?

- ☐ A Cartilage defects are more common among men
- ☐ B Even full-thickness cartilage defects with subchondral cortical bone defects do not predict a higher risk of knee pain
- ☐ C Cartilage defects correlate well with bone marrow lesions (BMLs)
- ☐ D Any association between cartilage defects and knee pain is mediated by BMLs

3 Which of the following statements regarding other variables which might influence pain in this patient's knee is most accurate?

- ☐ **A** Body mass index (BMI) is most strongly associated with diffuse knee pain
- ☐ **B** Any weight loss is associated a greater relative improvement in pain compared with increases in pain associated with weight gain
- ☐ **C** The vastusmedialis oblique is the muscle group most identified with knee pain
- ☐ **D** Cold weather accurately predicts a higher risk of knee pain

4 What can you tell this patient about OA pain in other parts of her body?

- ☐ **A** Grip strength does not predict hand pain
- ☐ **B** Radiographic changes do not predict hand pain
- ☐ **C** Joint-space narrowing of the hip is associated with the degree of pain
- ☐ **D** The biggest predictor of OA pain in the foot is female sex