Osteoarthritis

Factors associated with pain and implications for therapy

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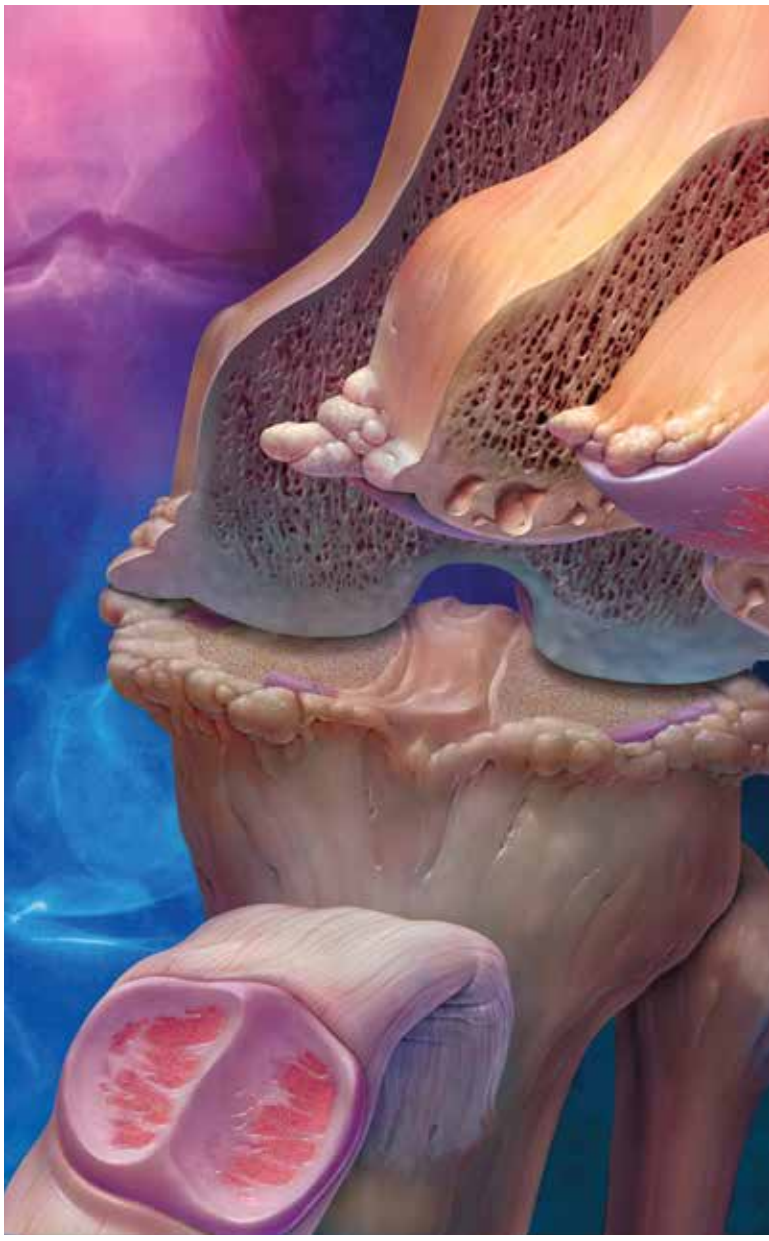
Osteoarthritis is the most common musculoskeletal cause of disability in western society. It should be regarded as an umbrella term for several pathways that result in pain and cartilage loss, which is leading to the development of pathophysiology-specific therapies. It is therefore important to try and pinpoint the causes of pain so treatment plans can be personalised for each affected patient.



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Osteoarthritis is the most common form of arthritis. It is a whole-joint problem leading to cartilage loss and, eventually, joint failure. It is one of the most common causes of pain, loss of function and disability in adults in Australia, and the incidence of this condition is increasing markedly due to an ageing population.

GPs are often the first point of contact for people experiencing pain and play a key role in managing patients with osteoarthritis. It is the pain that drives the patient to seek help and it is also pain that interferes with quality of life. A number of specialties can be consulted in the management of this condition, including physiotherapy, rheumatology, sports medicine, rehabilitation and orthopaedics.

This article reviews the factors associated with pain in osteoarthritis and discusses the implications of these findings for management, with a focus on the knee. Table 1 outlines the factors associated with pain and cartilage loss/damage.[1]

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Radiographs and knee pain

Overall, there is a modest but significant correlation between the degree of radiographic change and knee pain, which is most consistent for osteophytes. However, this correlation is not independent of muscle strength, obesity or several factors assessed on MRI scanning. This suggests that osteophytes may be a reflection of the disease process but not a key player in the generation of pain. It has also been suggested that the presence of osteophytes may be an attempt at repair.

MRI features and their association with knee pain

Bone marrow lesions, or bone marrow oedema, seen as increased water content or bright signal on fat-suppressed T2 MRI images (see Figure), have been recognised as a key feature of knee osteoarthritis. Several studies have linked bone marrow lesions with knee pain.[2] A significant correlation between change in bone marrow lesions and change in pain has been shown in both populations of patients in unselected community living and those with osteoarthritis suggesting a potential target for therapy.[2]

Indeed, a report of a proof-of-principle trial carried out only in patients with bone marrow lesions demonstrated that zoledronic acid (a potent bone-acting bisphosphonate used off label for osteoarthritis) could decrease both pain and size of bone marrow lesions over six months.[3] Another trial of chondroitin sulfate in patients with knee osteoarthritis showed a decrease in the size of bone marrow lesions over 12 months but no change in pain.[2]

Cartilage defects

Cartilage is aneural and therefore defects in cartilage should not be associated with pain. Despite this, there is consistent evidence that cartilage defects are probable indirect sources of pain mediated through local production of nociceptive substances. Cartilage defects correlate strongly with bone marrow lesions suggesting that bone marrow lesions and cartilage defects are closely related but both have independent associations with pain. Weight loss may improve defects and, therefore, reduce pain. Therapies aimed at cartilage have generally been unsuccessful.

Meniscal pathology

The association between meniscal pathology (i.e. the cushion between the cartilage surfaces in some joints such as the knee) and pain remains controversial and may reflect site-specific associations such as proximity to the neurovascular bundle. Weight loss may slow cartilage loss in people with a meniscal tear.

Key points

- **Osteoarthritis is an umbrella term for several active processes that lead to pain and/or cartilage loss.**
- **X-rays give limited information about osteoarthritis and only provide marginal assistance at tailoring therapy for the individual. MRI has great potential in this regard but targeted trials have been few to date.**
- **Bone marrow lesions and cartilage defects have independent associations with pain in people with osteoarthritis.**
- **Obesity and weak muscles are also independently associated with pain in osteoarthritis; therefore, weight loss and strengthening and aerobic exercises may help improve symptoms.**
- **Pain in osteoarthritis is also modified by central factors such as depression, catastrophisation, self-efficacy and a positive attitude.**
- **Targeting subchondral bone has the most potential to modify osteoarthritis given the failure of most therapies aimed at cartilage.**

Inflammation

Local inflammation (measured as synovitis and/or effusions) is linked with pain and is common in people with osteoarthritis but is not as severe as in those with rheumatoid arthritis. Furthermore, changes in synovitis (but not effusion severity) were associated with fluctuations in knee pain in patients with knee osteoarthritis in two studies suggesting that synovitis may be the key factor and effusion a consequence of synovitis.[2] Systemic inflammation is also important for knee pain and this opens up a number of options for therapies.

Corticosteroid injections are effective for pain in people with knee osteoarthritis and are recommended by most guidelines.[4] The evidence for this suggests a moderate benefit (Table 2) with an excellent safety profile. My practice and the data suggest up to four injections a year is safe.[5] Corticosteroid injections seem to be most effective for effusions thus it would seem logical to preferentially give corticosteroid injections to those patients with effusions.

NSAIDs help manage pain in patients with osteoarthritis but there are limited data on who may benefit most from taking these agents. Diacerein blocks interleukin-1 and is modestly effective for osteoarthritis pain but is not currently available in Australia.[4]

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.[2]

Table 1. Factors associated with knee pain and cartilage loss/damage or progression of osteoarthritis[1,2]

Factor	Associated with knee pain	Associated with cartilage loss/damage or progression of osteoarthritis
Bone marrow lesions	Yes	Yes
Cartilage defects	Yes	Yes
Meniscal tear	Yes	Yes
Meniscal extrusion	No	Yes
Effusion/synovitis	Yes	Yes
Osteophytes	Yes*	Yes*
Subchondral bone density	No	Yes
Tibial plateau area	No	Yes
Popliteal cysts	Yes*	No
Infrapatellar fat pad area/pathology	Yes	No
Bone attrition	Yes	No
Muscle strength	Yes	Yes
Physical activity	Yes (good for symptoms)	Yes (detrimental in abnormal joints)
Inflammation	Yes	Yes
Vitamin D deficiency	Yes	Yes
Obesity	Yes	Yes
Genes	Yes	No
Central factors	Yes	No

* Not independent of other factors.
Modified from Jones G. Int J Clin Rheumatol 2013; 8: 335-346.[2]

Figure. MRI scan showing common features of osteoarthritis including a large bone marrow lesion in femur (arrow), suprapatellar effusion, synovitis in the fat pad, macerated cartilage in the patellofemoral joint and increased signal in the posterior horn of the meniscus.

Other factors associated with knee pain

Obesity

Obesity is the strongest independent correlate of knee pain. There is level one evidence that weight loss improves knee symptoms;[4] however, interestingly weight gain is more strongly associated with worsening pain than weight loss is associated with improvements in pain implying limited reversibility. Nevertheless, in patients who are overweight with an apparently normal knee on examination and imaging, weight loss should be the main objective.

Weak muscles

Weak muscles are independently associated with pain in people with osteoarthritis, similar to the association of pain with obesity.

There is level one evidence that both strengthening and aerobic exercises help to manage pain in people with knee and hip osteoarthritis but the effect on structural progression is controversial.[4]

Central factors and genetics

Pain in people with osteoarthritis is also modified by central factors such as depression, catastrophisation (the tendency to view or present a situation as considerably worse than it actually is), self-efficacy and a positive attitude. Recently, there have been studies implicating specific genes associated with pain processing. These genes include *transient receptor potential cation channel subfamily V member 1* (*TRPV1*), *catechol-O-methyltransferase* (*COMT*) and *proprotein convertase gene 6* (*PCSK6*).[2]

Table 2. Effect size and level of evidence for pain relief with different osteoarthritis therapies[4]

Osteoarthritis therapy	Best evidence up to 2006		Best evidence up to 2009	
	Effect size (95% CI)	Level of evidence	Effect size (95% CI)	Level of evidence
Self-management	0.06 (0.02, 0.10)	1a	0.06 (0.02, 0.10)	1a
Education/information	0.06 (0.02, 0.10)	1a	0.06 (0.03, 0.10)	1a
Strengthening exercise	0.32 (0.23, 0.42)	1a	0.32 (0.23, 0.42)	1a
Aerobic exercise	0.52 (0.34, 0.70)	1a	0.52 (0.34, 0.70)	1a
Exercise for hip osteoarthritis	N/A	N/A	0.38 (0.08, 0.68)	1a
Aquatic exercise	0.25 (0.02, 0.47)	1b	0.19 (0.04, 0.35)	1a
Weight reduction	0.13 (-0.12, 0.36)	1b	0.20 (0.00, 0.39)	1a
Acupuncture	0.51 (0.23, 0.79)	1b	0.35 (0.15, 0.55)	1a
Electromagnetic therapy	0.77 (0.36, 1.17)	1a	0.16 (-0.08, 0.39)	1a
Acetaminophen	0.21 (0.02, 0.41)	1a	0.14 (0.05, 0.22)	1a
NSAIDs	0.32 (0.24, 0.39)	1a	0.29 (0.22, 0.35)	1a
Topical NSAIDs	0.41 (0.22, 0.59)	1a	0.44 (0.27, 0.62)	1a
Opioids	N/A	N/A	0.78 (0.59, 0.98)	1a
Intra-articular corticosteroids	0.72 (0.42, 1.02)	1a	0.58 (0.34, 0.75)	1a
Hyaluronate	0.32 (0.17, 0.47)	1a	0.60 (0.37, 0.83)	1a
Glucosamine sulfate	0.61 (0.28, 0.95)	1a	0.58 (0.30, 0.87)	1a
Glucosamine hydrochloride	N/A	N/A	-0.02 (-0.15, 0.11)	1b
Chondroitin sulfate	0.52 (0.37, 0.67)	1a	0.75 (0.50, 1.01)	1a
Diacerein*	0.22 (0.01, 0.42)	1b	0.24 (0.08, 0.39)	1b
Avocado soybean unsaponifiable*	N/A	N/A	0.38 (0.01, 0.76)	1a
Rose hip	N/A	N/A	0.37 (0.13, 0.60)	1b
Lavage/debridement	0.09 (-0.27, 0.44)	1b	0.21 (-0.12, 0.54)	1b

Reproduced with permission from Zhang W, et al. Osteoarthritis Cartilage 2010; 18: 476-499.[4]

Note: A small effect size is 0.2, a moderate effect size is 0.5 and a large effect size is 0.8. One can see that paracetamol/acetaminophen has a very small effect size. NSAIDs are small to moderate and opioids are large (although a recent paper suggests this may be inflated).

* Not available in Australia.

Abbreviations: CI = confidence interval; N/A = data not available.

There are limited data about the treatment of these central factors in people with osteoarthritis; however, there is evidence suggesting that duloxetine (a serotonin and noradrenaline reuptake inhibitor that is used off label for osteoarthritis) has a modest but significant effect on pain in people with knee osteoarthritis.[5]

Weather

One of the best studies investigating weather and knee pain included 200 participants who had knee osteoarthritis and independently collected meteorological data that participants were not aware of.[6] Although the connection between weather and symptoms was originally considered to be an urban myth, this study found consistent associations between pressure change and ambient temperature with pain severity and suggestive data for dewpoint (the atmospheric temperature varying according to pressure and humidity) below which water droplets begin to condense and dew can form.

Managing a woman with mechanical knee pain and swelling

Case history

A 68-year-old woman, who is a retired secretary, presents with a three-year history of progressive mechanical knee pain and swelling. There is some night pain and morning stiffness of five minutes. Prior to your consultation, she has tried extended-release paracetamol, glucosamine sulfate, rose hip vital, chondroitin, fish oil, physiotherapy, aqua aerobics, conservative weight loss programs and ibuprofen (in doses up to 800 mg/day). None have been particularly beneficial. She finds it difficult to walk more than 200 metres and cannot climb stairs. She has a background history of hypertension (well controlled with an ACE inhibitor and a diuretic), chronic stable angina, obesity (body mass index of 38 kg/m^2) and she smokes 20 cigarettes daily. There is a strong family history of lupus in her sister and aunt.

Examination

Examination shows an overweight woman with a full range of movement in both knees. She has small effusions, crepitus on movement and some medial bony enlargement with tenderness. Her muscles seem a little weak. Hip movements are normal. She has Heberden's nodes in the fingers but these are not painful. Radiographs of her knees show no joint space narrowing. Basic blood tests are normal including erythrocyte sedimentation rate, C-reactive protein, creatine kinase, antinuclear antibodies and rheumatoid factor.

Initial treatment strategies

You diagnose osteoarthritis of the knees based on clinical criteria only and consider a number of initial management strategies. NSAIDs in therapeutic doses are risky given her antihypertensive regimen and angina. You therefore decide to drain 30 mL of fluid from her knees (which has no crystals) and give her intra-articular corticosteroid injections (e.g. 80 mg methylprednisolone) into each knee. The evidence for this suggests a moderate benefit (Table 2) with an excellent safety profile. There is controversy about the duration of response, but in this case the corticosteroid injections give her 10 weeks of pain relief so you repeat this regimen approximately every three months as there are data that this is safe to use for up to two years.[7]

After one year, the injections stop helping so you decide that further injections are unlikely to be worthwhile. She asks what other options are available. You discuss surgically-assisted weight loss and joint replacement but she is not interested in these options. She is interested in a trial of zoledronic acid based on a recent publication she has read so you refer her to a rheumatologist.

Further treatment strategies

The rheumatologist explains to her that zoledronic acid is not subsidised by the Pharmaceutical Benefits Scheme and is not yet a mainstream therapy for people with osteoarthritis but shows some promise. Despite the normal x-ray, an MRI scan shows a large femoral lesion (Figure) as well as a number of other pathological changes. The patient decides to go ahead with zoledronic acid therapy and obtains it by private script. Three months after receiving the therapy, a repeat MRI scan shows total resolution of the bone marrow lesion, which is rare based on natural history studies. However, with this there has been only a modest improvement in pain.

This patient has now failed most recognised conservative therapies and so you again discuss the options with her. Lap banding (available for relief of joint pain on the Medicare Benefits Schedule) may be more appropriate than joint replacement or opioids in this case given the significant obesity, the relatively mild joint changes and the literature suggesting overweight people have less successful joint replacement outcomes.

Outcome

She agrees to undergo lap banding and loses 25 kg over 18 months. Her pain score is now 3/10. She is taking no pain medications and is participating in all the activities she wants to do. You leave follow up open depending on progress.

Conclusion

Pain in people with osteoarthritis is clearly multifactorial and treatment will differ according to the patient-specific cause. It is therefore ideal to assess each patient to plan an individualised treatment approach (see the Box for an individualised management plan of a 68-year-old woman with knee pain and swelling). **PMT**

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Case Study on page 31.