Acute and chronic pain in orthopaedic and rheumatologic diseases: mechanisms and characteristics

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ABSTRACT

Pain is one of the most frequent clinical symptoms encountered by orthopaedic surgeons and rheumatologists as it is one of the main reasons for patients seeking medical help. Traumas and/or inflammatory rheumatologic diseases give rise to two different types of acute pain, but their chronic evolution is so similar that they both need to be treated as early as possible. It is now widely accepted that chronic pain is a disease per se, and that its location may be less important than the way in which it is perceived by people suffering from it. Consequently, its pharmacological and non-pharmacological treatment should be based on its specific characteristics, other disease-related factors, the ability of patients to cope with it, and the way in which they live their lives.

Introduction

The pain associated with many orthopaedic and rheumatologic conditions is the result of a variety of genetic, biological, psychological and social factors, and physiological interactions between the central nervous system (CNS) and the peripheral nervous systems (1, 2). Acute pain is primarily attributable to inflammation and/or peripheral structural damage, whereas chronic pain (generally defined as lasting ≥3 months) is more usually due to signals arising from the CNS (2).

Types of pain

Acute or chronic pain is one of the most frequent clinical symptoms encountered by orthopaedic surgeons or rheumatologists, and the most frequent reason why patients seek medical help.

Acute pain

Acute orthopaedic pain is caused by tissue damage activating nociceptors, and is closely related to trauma, *i.e.* "damage directly or indirectly caused by an external force, with or without the disruption of structural continuity", such as that caused by domestic or road accidents, sports injuries, or bodily assault (3). An acute orthopaedic trauma often requires hospitalisation (4), where treatment primarily consists of repairing the injury rather than treating pain, even though acute trauma pain is often persistent and associated with pain-related disability (5).

On the other hand, rheumatological pain is frequently considered a marker of inflammation, although its intensity only weakly correlates with peripheral inflammation measures (6); however, pain is associated with disease activity, and radiographic changes may predict future pain (7, 8). Inflammation causes pain, stiffness and progressive joint damage, but it is becoming increasingly possible to completely suppress it and ensure clinical remission (9), and long-term outcomes may be improved if this is done rapidly (10). Treatment with conventional and biological disease-modifying anti-rheumatic drugs (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs) is effective in reducing the symptoms of inflammatory pain (11), although many patients continue to experience moderate pain because of alterations in the mechanisms that regulate central pain, such as those with chronic widespread pain (CWP) characterising fibromyalgia (FM) (1, 2). Non-inflammatory pain may affect the assessment of disease activity or anatomical damage, and so the aim of treatment is not only to control inflammatory disease and repair anatomical damage, but also to relieve painful symptoms.

Chronic pain

It is now widely believed that local or widespread chronic pain triggered by an initial peripheral injury or inflammation, is a disease per se, and that its

location may be less important than the way in which it is perceived by people suffering from it (1, 12).

Neuroplastic changes in the CNS can increase pain transmission (1, 12), leading to hyperalgesia (an increased sensation of pain in response to normally painful stimuli) and/or allodynia (pain in response to normally non-painful stimuli). The complex mechanisms giving rise to CWP include temporal summation (wind-up), long-term potentiation, heterosynaptic potentiation, dysfunctional descending pain inhibition, and activation of the descending facilitatory pathway (12). It may therefore be necessary to consider the centralised aspects of pain when administering antinociceptive medications.

Pain mechanisms

The causes of inflammatory pain in patients with rheumatoid arthritis (RA) may vary from person to person, and be different in early and late disease, or during and between inflammatory flares. Inflamed synovium generates prostaglandins and bradykinin, pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and IL-6, and nerve growth factor beta (NGF-β), all of which sensitise the peripheral nerves (13-16).

However, the synovium is probably not the only source of pain as the joint capsule, ligaments, the outer regions of the menisci, subchondral bone, tendon sheaths, and muscles all contain sensory nerves (13).

Synovitis is associated with alterations in the expression of neurotransmitters, such as γ-aminobutyric acid (GABA), substance P and calcitonin gene-related peptide (CGRP), and their receptors in the spinal cord (16). Activated spinal microglia and astrocytes produce pain-transmitting cytokines (TNF-α, IL-1 and IL-6), and transmission may be further increased by greater descending activation, less descending inhibition, and reduced pain thresholds in adjacent tissues (17).

Bones, muscles and ligaments respond differently to acute trauma, giving rise to pain due to nociceptive, ischemic and inflammatory mechanisms, as well as nerve damage (12). Nociceptive pain is due to the activation of peripheral pain receptors (nociceptors) during surgery or trauma, whereas inflammatory pain is a response to tissue injury that releases inflammatory mediators from damaged cells (histamine, bradykinin, etc.) and attracts pro-inflammatory cytokines (TNF-a, IL-1b, IL-6) released by immune cells (PMNs, macrophages, etc.) to the site of the injury, where they reduce nociceptor thresholds. Nerve injury leads to neuropathic pain and other sensory abnormalities (12). Tissue injury and local inflammation induce hyperalgesia and allodynia, both of which are caused by a combination of peripheral nociceptor sensitisation and facilitated pain processing inside the spinal cord and higher in the CNS. It must also be remembered that recovery from orthopaedic damage does not necessarily mean that the pain will disappear because anoxia with the release of nitric oxide (NO), blood-filled tissue, and the proprioceptive and nocireceptive alterations caused by anatomical damage may cause it to perist (18, 19).

The role of centralised pain in rheumatic and orthopaedic diseases

Collaboration between anesthesists and orthopaedic surgeons has become increasingly important (20) because the challenge of preventing persistent post-surgical pain is seen as an index of the quality of health care. For example, although many studies have demontrated improvements in pain, function and the quality of life, up to 20% of patients undergoing total knee arthroplasy (TKA) experience post-surgical pain for six months or more (21).

As many as 15-30% of patients with classic autoimmune or rheumatic disorders also have what was once called "secondary FM" (20). As this is much higher than the 2% prevalence of FM in the general population, it seems that it may be caused by the pain and/or stress accompanying chronic rheumatic diseases (22).

Most chronic pain patients are women, who underwent an early-life trauma, and have a history of chronic pain or centrally mediated symptoms such as insomnia, fatigue, memory problems and mood disturbances, all of which increase the probabilty that acute pain will become chronic (23, 24). Immunological cascades may play a role in maintaining central sensitivity and chronic pain, which is increased when CNS glial cells release pro-inflammatory cytokines, and so the traditional dichotomy of inflammatory vs non-inflammatory pain may no longer be appropriate (20).

Pain in rheumatic or orthopaedic conditions

Identifying subsets of patients with different rheumatic or orthopaedic diseases and prominent CNS factors might help to solve an old dilemma (23, 24). Peripherally based models clearly cannot explain much of the variance in pain, fatigue, sleep, memory problems and functional disabilities that are not caused by peripheral factors alone: for example, although the joints and surrounding structures are the pathological foci of osteoarthritis (OA), patients with knee OA frequently experience pain in unaffected areas (25), and many of the same patients find fatigue more functionally limiting than pain (25). Peripherally based theories alone cannot explain why these symptoms are so common and often refractory to standard therapies (2).

Furthermore, patients with severe, unremitting pain in a single joint obtain considerable relief from total joint replacement surgery (26), and the quality of life of many patients has been improved by the introduction of treatments that suppress underlying inflammatory disease. However, both solutions are expensive (27), 15% of the patients undergoing total knee replacement continue to experience disabling pain, and up to 25% of patients with active RA receive no significant benefit from anti-TNF therapy.

Impact of pain on the quality of life

Any type of peripheral pain should be treated appropriately and rapidly because the likelihood of developing chronic pain is related to the duration of the peripheral pain stimulus. A minority of patients may not find pain a

problem because it disappears when the underlying rheumatic or orthopaedic disease is properly treated (28). However, others with a disease of nociceptive origin find that the spread of multifocal pain or FM becomes their major symptom even when the underlying disease is controlled (29).

Treatment

Pharmacological and non-pharmacological treatment should be based on its specific characteristics, other disease-related factors, the ability of patients to cope with it, and the way in which they live their lives (11). If chronic pain is inadequately treated, many patients cannot take part in everyday activities, their ability to work is affected, and they often suffer fron depression and anxiety (30). Paracetamol and NSAIDs are still used to treat chronic pain in patients with rheumatic or orthopaedic diseases, but it is becoming increasingly clear that non-selective NSAIDs and selective cyclo-oxygenase 2 inhibitors can have toxic effects (11, 30, 31). This is particularly important in the case of the elderly, who frequently have more significant problems than younger patients, and are at high risk of NSAID-related adverse events. If paracetamol and other non-opioid analgesics are ineffective or not tolerated, it may be more appropriate to administer mild opioids (codeine or tramadol) or strong opioids, such as morphine, hydromorphone or oxycodone, associated with naloxone (in order to reduce adverse events) or paracetamol in order to increase analgesia (30, 31).

Our limited understanding of the aetiology of CWP or FM, and the patients' poor response to conventional treatments, makes it especially difficult to treat in patients with rheumatic and orthopaedic diseases.

FM is one of the most common causes of chronic widespread pain. It is characterised by reduced pain thresholds (hyperalgesia) and pain with normally innocuous stimuli (allodynia) (1). FM is common with a prevalence of 2% in the general population (32). However, its diagnosis and management remain a challenge for patients and healthcare professionals. The diagnosis of FM often takes more than 2 years with an average of 3.7 consultations with different physicians. Although pain is the dominant symptom in FM, other symptoms such as fatigue, non-refreshed sleep, mood disturbance and cognitive impairment are common (1). Patients with FM have diverse combinations and varying degrees of severity of these symptoms (34, 35). Approximately 50% of all patients have difficulty with routine daily activities while 30%-40% have to stop work or change the type of work they do. The societal cost of FM due to reduced productivity is high. As FM is a complex syndrome associated with a wide range of symptoms, treatment should be tailored to the individual, addressing their particular needs and targeting their most distressing symptoms. The best strategy is to use a multidisciplinary approach to treatment, using both pharmacological and non-pharmacological interventions as required (35, 36).

As it has been shown that tricyclic antidepressants, selective serotonin reuptake inhibitors, and dual serotonin and norepinephrine inhibitors can be useful in patients with FM, they may also be useful in patients with rheumatic and orthopaedic diseases who experience pain that is not due to mechanical or inflammatory causes, although only a few respond to these treatments alone (35, 37).

Cannabis has been used for millennia to reduce pain and other somatic and psychological symptoms. There are few evidences on the effectiveness of cannabinoids in the improvement of FM or CWP symptoms. A recent Cochrane review that included two studies with 72 participants, comparing nabilone (a synthetic cannabinoid with a bedtime dosage of 1 mg/day) to placebo and/or to amitriptyline, showed that no studies reported evidence indicating greater reduction of pain and improvement in limitations of quality of life (38). Moreover, there were no significant differences to placebo for fatigue and depression, and moderate better effects of nabilone on sleep vs amitriptyline. In conclusion, they found no relevant studies with herbal cannabis, plant-based cannabinoids or synthetic cannabinoids other than nabilone in FM (38). A cannabinoid (Cannabis flos 19%), containing tetrahydrocannabinolic acid 19% and cannabidiolic acid <1% used orally as a decoction, is available in Italy for treating chronic pain.

Girardi *et al*. (39) evaluated the effect of cannabis flos 19% in 15 patients affected by FM according to the ACR 2010 criteria (30 mg twice a day for the first month followed by 60 mg twice a day) and showed that cannabis flos 19% is effective in improving pain, fatigue, anxiety and depression in FM patients. Given these data, further studies are suggested in order to confirm this preliminary results on the efficacy and safety of this therapy for treating patients with primary FM and FM or/and CWP associated to orthopaedic and rheumatic diseases.

Appropriate pain relief requires an understanding of individual needs, and patients with rheumatic or orthopaedic pain or FM-associated pain can also be helped by non-pharmacological approaches, including exercise, cognitive behavioural therapy, homeopathy, physiotherapy, acupuncture, magnetism, dietary alterations, laser therapy and hyperbaric oxygen therapy (HBOT) (35).

HBOT is the therapeutic administration of 100% oxygen at environmental pressures of more than one atmosphere absolute (ATA). It involves placing a patient in an airtight vessel, increasing the internal pressure, and administering 100% oxygen for respiration in order to deliver a greatly increased partial pressure of oxygen to the tissues. Treatments tipically involve pressurisation between 1.5 and 3.0 ATA for between 60 and 120 minutes once or more times a day. There is a body of evidence supporting the use of HBOT to decrease inflammation and pain behaviours in rodents, but there is a lack of evidence concerning its clinical usefulness in human pain conditions (40, 41). However, Yildiz *et al*. (42) found that HBOT significantly reduced the number and threshold of tender points, and an Israeli group has recently shown that it can improve the symptoms and quality of life of FM patients and used SPECT to show that it can induce

neuroplasticity and significantly rectify abnormal brain activity in pain-related areas (43). Based on these data, HBOT could be useful also in patients affected by FM or CWP associated with orthopaedic and rheumatic diseases such as RA, OA, etc.

Finally, these interventions are generally safe and therefore their long-term use is not detrimental. Furthermore, as some form of physical activity is essential for the health of all patients with musculoskeletal disorders, it can have many beneficial physical and mental effects on patients with chronic pain and FM (35).

Conclusions

It is still unknown why chronic pain remains localised in some patients with rheumatic or orthopaedic diseases, but becomes widespread/FM in others. The obvious risk factors include genetics, age, gender, co-morbidities, traumas and individual characteristics, but there are no specific clinical, laboratory or neuroimaging markers that can indicate why and when localised pain evolves into CWP. Any clinical evaluation should include an assessment of the intensity and localisation of pain, which should always be treated promptly to prevent it from becoming chronic. Treatment should be based on an integrated strategy that takes into account the characteristics of the pain itself, its peripheral pattern and centralisation in individual patients, and the psychosocial factors affecting their pain responses. Whether or not it is associated with a post-trauma anatomical lesion or with an inflammatory rheumatic disease leading to joint degeneration, it is first necessary to determine whether it is mechanical, chemical and/or neurological in nature in order to be able to intervene early. This may be done directly (surgically or otherwise) with the aim of restoring normal anatomical relationships and/or pharmacologically with the aim of rebalancing normal psycho-physical functions. In particular, consideration must be given to any comorbidities and/or previous mental states, and their likelihood of contributing to the chronicity and/or self-maintenance of the pain.

References

1. STISI S, CAZZOLA M, BUSKILA D *et al*.: Italian Fibromyalgia Network. Etiopathogenetic mechanisms of fibromyalgia syndrome. *Reumatismo* 2008; 60 (Suppl. 1): 25-35.
2. PHILLIPS K, CLAUW DJ: Central pain mechanisms in the rheumatic diseases: future directions. *Arthritis Rheum* 2013; 65: 291-302.
3. BERBEN SA, MEIJS TH, VAN DONGEN RT *et al*.: Pain prevalence and pain relief in trauma patients in the Accident & Emergency department. *Injury* 2008; 39: 578-85.
4. BRADLEY C, HARRISON J: Descriptive Epidemiology of Traumatic Fractures in Australia. Canberra: Australian Institute of Health and Welfare, 2004.
5. CLAY FJ, WATSON WL, NEWSTEAD SV, MCCLURE RJ: A systematic review of early prognostic factors for persisting pain following acute orthopaedic trauma. *Pain Res Manag* 2012; 17: 35-44.
6. KHAN NA, SPENCER HJ, ABDA E *et al*.: Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res* 2012; 64: 206-14.
7. COURVOISIER N, DOUGADOS M, CANTAGREL A *et al*.: Prognostic factors of 10-year radiographic out- come in early rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2008; 10: R106.
8. SARZI-PUTTINI P, FIORINI T, PANNI B, TURIEL M, CAZZOLA M, ATZENI F: Correlation of the score for subjective pain with physical disability, clinical, and radiographic scores in recent onset rheumatoid arthritis. *BMC Musculoskelet Disord* 2002; 3: 18.
9. SCHIPPER LG, FRANSEN J, DEN BROEDER AA, VAN RIEL PL: Time to achieve remission determines time to be in remission. *Arthritis Res Ther* 2010; 12: R97.
10. FINCKH A, CHOI HK, WOLFE F: Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. *Ann Rheum Dis* 2006; 65: 1192-7.
11. WHITTLE SL, COLEBATCH AN, BUCHBINDER R *et al*.: Multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis: integrating systematic literature research and expert opinion of a broad panel of rheumatologists in the 3e Initiative. *Rheumatology* (Oxford) 2012; 51: 1416-25.
12. WOOLF CJ: Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 2010; 152: S2-15.
13. KONTTINEN YT, TIAINEN VM, GOMEZ-BARRENA E, HUKKANEN M, SALO J: Innervation of the joint and role of neuropeptides. *Ann N Y Acad Sci* 2006; 1069: 149-54.
14. RAYCHAUDHURI SP, RAYCHAUDHURI SK, ATKURI KR, HERZENBERG LA, HERZENBERG LA: Nerve growth factor: a key local regulator in the pathogenesis of inflammatory arthritis. *Arthritis Rheum* 2011; 63: 3243-52.
15. SCHAIBLE HG, VON BANCHET GS, BOETTGER MK *et al*.: The role of proinflammatory cytokines in the generation and maintenance of joint pain. *Ann N Y Acad Sci* 2010; 1193: 60-9.
16. BENEMEI S, NICOLETTI P, CAPONE JG, GEPPETTI P: CGRP receptors in the control of pain and inflammation. *Curr Opin Pharmacol* 2009; 9: 9-14.
17. SCHAIBLE HG, EBERSBERGER A, VON BANCHET GS: Mechanisms of pain in arthritis. *Ann N Y Acad Sci* 2002; 966: 343-54.
18. JEFFREY MAN HS, TSUI AK, MARSDEN PA: Nitric oxide and hypoxia signaling. *Vitam Horm* 2014; 96: 161-92.
19. MC MAHON SB: Wall and Melzack's Texbook of pain. 6th ed. Philadelphia, PA: Elsevier/Saunders; 2013: xxix, pp 1153.
20. GROSU I, DE KOCK M: New concepts in acute pain management: strategies to prevent chronic postsurgical pain, opioid- induced hyperalgesia, and outcome measures. *Anesthesiol Clin* 2011; 29: 311-27.
21. GROSU I, LAVAND'HOMME P, THIENPONT E: Pain after knee arthroplasty: an unresolved issue. *Knee Surg Sports Traumatol Arthrosc* 2014; 22: 1744-58.
22. ATZENI F, MASALA IF, SALAFFI F, DI FRANCO M, CASALE R, SARZI-PUTTINI P: Pain in systemic inflammatory rheumatic diseases. *Best Pract Res Clin Rheumatol* 2015; 29: 42-52.
23. GOESLING J, CLAUW DJ, HASSETT AL: Pain and depression: an integrative review of neurobiological and psychological factors. *Curr Psychiatry Rep* 2013; 15: 421.
24. CLAY FJ, WATSON WL, NEWSTEAD SV, MCCLURE RJ: A systematic review of early prognostic factors for persisting pain following acute orthopedic trauma. *Pain Res Manag* 2012; 17: 35-44.
25. CLAUW DJ, WITTER J: Pain and rheumatology: thinking outside the joint [editorial]. *Arthritis Rheum* 2009; 60: 321-4.
26. JOHN H, HALE ED, TREHARNE GJ, KITAS GD, CARROLL D: A randomized controlled trial of a cognitive behavioural patient education intervention vs a traditional information leaflet to address the cardiovascular aspects of rheumatoid disease. *Rheumatology* (Oxford) 2013; 52: 81-90.
27. CALDER JD, ASHWOOD N, HOLLINGDALE JP: Survivorship analysis of the "Performance" total knee replacement-7-year follow-up. *Int Orthop* 1999; 23: 100-3.
28. SARZI-PUTTINI P, ATZENI F, CLAUW DJ, PERROT S: The impact of pain on systemic rheumatic diseases. *Best Pract Res Clin Rheumatol* 2015; 29: 1-5.
29. LEVY O, SEGAL R, MASLAKOV I, MARKOV A, TISHLER M, AMIT-VAZINA M: The impact of concomitant fibromyalgia on visual analogue scales of pain, fatigue and function in patients with various rheumatic disorders. *Clin Exp Rheumatol* 2016; 34 (Suppl. 96): S120-4.
30. CHERUBINO P, SARZI-PUTTINI P, ZUCCARO SM, LABIANCA R: The management of chronic pain in important patient subgroups. *Clin Drug Investig* 2012; 32 (Suppl. 1): 35-44.
31. SARZI-PUTTINI P, VELLUCCI R, ZUCCARO SM, CHERUBINO P, LABIANCA R, FORNASARI D: The appropriate treatment of chronic pain. *Clin Drug Investig* 2012; 32 (Suppl. 1): 21-33.
32. JONES GT, ATZENI F, BEASLEY M, FLÜß E, SARZI-PUTTINI P, MACFARLANE GJ: The

prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. *Arthritis Rheumatol* 2015; 67: 568-75.
33. BAZZICHI L, GIACOMELLI C, CONSENSI A et al.: One year in review 2016: fibromyalgia. *Clin Exp Rheumatol* 2016; 34 (Suppl. 96): S145-9.
34. TALOTTA R, ATZENI F, BAZZICHI L *et al*.: Algo-dysfunctional syndromes: a critical digest of the recent literature. *Clin Exp Rheumatol* 2015; 33 (Suppl. 88): S102.
35. MACFARLANE GJ, KRONISCH C, DEAN LE *et al*.: EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017; 76: 318-28.
36. GERARDI MC, BATTICCIOTTO A, TALOTTA R, DI FRANCO M, ATZENI F, SARZI-PUTTINI P: Novel pharmaceutical options for treating fibromyalgia. *Expert Rev Clin Pharmacol* 2016; 16: 1-7.
37. ATZENI F, SALLÌ S, BENUCCI M, DI FRANCO M, ALCIATI A, SARZI-PUTTINI P: Fibromyalgia and arthritides. *Reumatismo* 2012; 64: 286-92.
38. WALITT B, KLOSE P, FITZCHARLES MA, PHILLIPS T, HÄUSER W: Cannabinoids for fibromyalgia. *Cochrane Database Syst Rev* 2016; 7: CD011694.
39. GERARDI MG, BATTICCIOTTO A, TALOTTA R, DITTO MC, ATZENI F, SARZI-PUTTINI P: Efficacy of Cannabis flos in patients with fibromyalgia: a monocentric observational study. *Arthritis Rheumatol* 2016; 68 (Suppl. 10).
40. HUI J, ZHANG ZJ, ZHANG X, SHEN Y, GAO YJ: Repetitive hyperbaric oxygen treatment attenuates complete Freund's adjuvant-induced pain and reduces glia-mediated neuroinflammation in the spinal cord. *J Pain* 2013; 14: 747-58.
41. LIN KC, NIU KC, TSAI KJ *et al*.: Attenuating inflammation but stimulating both angiogenesis and neurogenesis using hyperbaric oxygen in rats with traumatic brain injury. *J Trauma Acute Care Surg* 2012; 72: 650-9.
42. YILDIZ S, KIRALP MZ, AKIN A *et al*.: A new treatment modality for fibromyalgia syndrome: hyperbaric oxygen therapy. *J Int Med Res* 2004; 32: 263-7.
43. EFRATI S, GOLAN H, BECHOR Y *et al*.: Hyperbaric oxygen therapy can diminish fibromyalgia syndrome--prospective clinical trial. *PLoS One* 2015; 10: e0127012.