Desirée Dorleijn

HIP OSTEOARTHRITIS

symptomatic presentation and non-operative treatment

Hip Osteoarthritis
symptomatic presentation and non-operative treatment

Desirée M.J. Dorleijn

The e-book version of this thesis is available at https://epubs.ogc.nl/?epub=d.dorleijn

Part of this thesis is based on the HOCI study. The HOCI study was funded by the Dutch Arthritis Foundation and Fonds NutsOhra.
Financial support for the publication of this thesis was kindly provided by:
Nederlandse Orthopaedische Vereniging, Anna Fonds | Noref, Erasmus MC afdeling huisartsgeneeskunde.

ISBN 978-94-6169-979-4
Layout and printed by: Optima Grafische Communicatie (www.ogc.nl)

Hip Osteoarthritis
symptomatic presentation and non-operative treatment

Heupartrose

symptomatische presentatie en conservatieve behandeling

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 25 januari 2017 om 11:30 uur

door

Desirée Maria Johanna Dorleijn
geboren te Vlissingen

Erasmus University Rotterdam

Promotiecommissie

Promotor
Prof.dr. S.M.A. Bierma-Zeinstra

Overige leden
Prof.dr. F.J.P.M. Huygen
Prof.dr. A.G. Vulto
Prof.dr. R.G.H.H. Nelissen

Copromotoren
Dr. P.A.J. Luijsterburg
Dr. P.K. Bos

Table of contents

Chapter 1	General introduction	7
Chapter 2	Effectiveness of intramuscular corticosteroid injection versus placebo injection in patients with hip osteoarthritis: design of a randomized double-blinded controlled trial	19
Chapter 3	Intramuscular corticosteroid injection versus placebo injection in hip osteoarthritis: a 12 week blinded randomized controlled trial	31
Chapter 4	Is anesthetic hip joint injection useful in diagnosing hip osteoarthritis? A meta-analysis of case series	53
Chapter 5	Association between biochemical cartilage markers and clinical symptoms in patients with hip osteoarthritis: cohort study with two-year follow-up	71
Chapter 6	Associations between weather conditions and clinical symptoms in patients with hip osteoarthritis: A two-year cohort study	87
Chapter 7	Greater trochanter pain syndrome: prevalence and influence on hip pain severity in patients with hip osteoarthritis in a cohort study	105
Chapter 8	General discussion	119
	Summary	133
	Nederlandse samenvatting	141
	Dankwoord	149
	Curriculum Vitae	155
	PhD portfolio	159
	List of publications	163

CHAPTER 1

General introduction

General introduction

Osteoarthritis (OA) is a common, chronic joint disease occurring (mostly) in middle-aged and elderly persons, and characterized by pain and disability. Knee, hand and hip are the joints most commonly affected by OA and registered in general practice.[1, 2] Although OA is not a life-threatening disease, the symptoms of pain and disability can have considerable impact on a person's activities of daily living. The global burden of knee and hip OA has recently been compared to other diseases in which the burden of the diseases was measured by means of Years Lived with Disability (YLD).[3] Hip and knee OA were ranked as the 11th highest contributor to global disability (of the 291 diseases studied); from 1990 to 2010 the YLD for hip and knee OA increased from 10.5 million to 17.1 million and was the fastest increasing contributor.[3] In the last 20 years the prevalence of OA has risen by 24% in males and by 17% in females.[4] Moreover, healthcare costs in the Netherlands have almost doubled from 530.5 million in 2003 to 1.1 billion in 2011. Hospital care, including joint replacement, accounts for most of these costs (54%).[5] Due to an aging society and an increase in obesity the incidence of OA will further increase, with an estimated rise of almost 40% between 2011 and 2030.[6]

OA is characterized by a slowly progressive change of synovial joint tissues, including cartilage destruction and alterations of the bone and synovial tissue. The main characteristics of OA are cartilage loss, formation of new bone at the joint margins (osteophytes), increased thickening of the bone structure (subchondral sclerosis) and cyst formation.[7] Patients with OA generally suffer from joint pain, tenderness, limited joint motion, disability, crepitus, and swelling of the affected joint.[7]

Hip osteoarthritis

Hip OA is a common musculoskeletal disease in the Netherlands with a prevalence of 9.6/1000 in males and 19.6/1000 in females, and an incidence of 0.9 in males and 1.6 in females.[8] Currently, because no treatment is available that can cure OA, the treatment of OA consists of the management of symptoms. In the Netherlands, the treatment of symptomatic hip OA begins in primary care. When symptoms progress and joint arthroplasty becomes an option, patients are usually referred to an orthopaedist. Patients with incident hip OA remain in primary care for (on average) 7 years until referral to an orthopaedic specialist.[9] Many patients with end-stage hip OA undergo total hip replacement (THR); in 2014 in the Netherlands a total of 28,026 THR procedures were performed.[10]

Diagnosis

Hip OA can usually be diagnosed based on clinical findings.[8, 11] For research and inclusion of patients in clinical trials, it is advised to use the established criteria for the classification of OA.[12] For hip OA the American College for Rheumatology classification tree is most often used (Figure 1).[13]

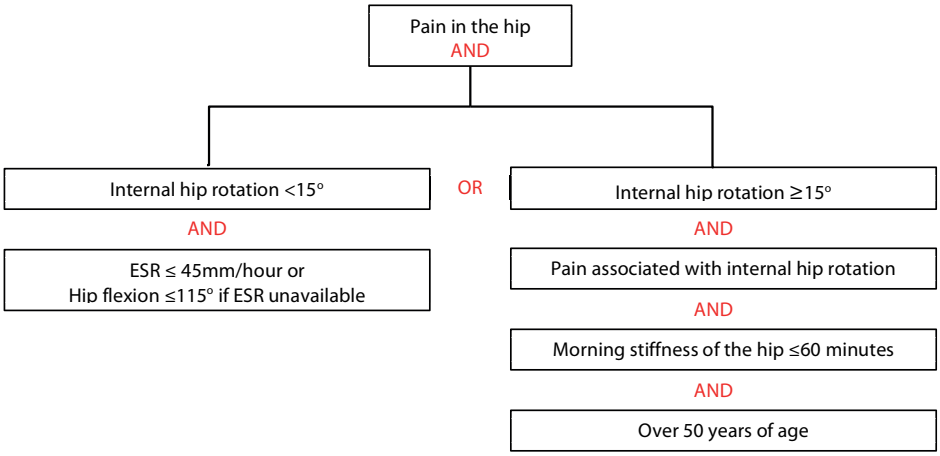


Figure 1 Classification tree for hip OA according to the American College for Rheumatology.[13]
ESR = Erythrocyte Sedimentation Rate

Radiographic hip OA can be graded with the Kellgren and Lawrence (KL) score, ranging from 0 to 4.[14] On radiography, a hip joint without OA features scores KL 0 and a hip joint with severe OA scores KL 4. This KL score is often dichotomized between the absence of radiographic OA (KL 0 and 1) and the presence of radiographic OA (KL ≥2). However, although the severity of radiographic hip OA usually correlates well with the patient's reported symptoms, this relationship cannot be used for diagnostic purposes.[15-17]

Hip pain can also occur due to pathology other than OA in the hip joint, e.g. labral pathology, femoral head osteonecrosis, bone tumors, inguinal hernia, greater trochanter pain syndrome (GTPS), and radiating/radicular pain from the lumbosacral spine and sacroiliac joints.

Careful history taking and physical examination can often differentiate between hip OA and other sources.[13] However, when signs, symptoms and radiographs are atypical for hip OA, this can cause a diagnostic dilemma.[18]

To exclude or confirm an intra-articular source of hip pain, an intra-articular anesthetic hip injection can be performed as an additional diagnostic test.[19-22] Under fluoroscopic or ultrasound guidance the hip joint is injected with an anesthetic and the patient is asked to report the course of the severity of pain after injection. In case of an intra-articular cause of

hip pain, the pain should diminish or be absent after this injection for (at least) some hours. Although this diagnostic injection is widely used in orthopaedic practice, the diagnostic value of this injection is still debated. The studies that investigated the diagnostic value of this test included a small number of participants. Also, the results of these studies may be difficult to interpret because of problems related to the reference test used.[19-27]

Course of pain in hip OA

Patients with hip OA often show fluctuating pain levels. Periods of relatively mild pain are alternated with periods of pain flairs.[28, 29] Moreover, little is known about the mechanism behind these fluctuations in pain severity.[30]

Recently, biochemical markers have become a topic of research in OA. Biochemical markers, or biomarkers, are characteristics that are objectively measured and evaluated as an indicator of biologic or pathologic processes.[31] Biomarkers in OA originate from bone, synovial tissue, and articular cartilage and can be measured in serum, urine or synovial fluid.[32] Although much work has focused on biomarkers in knee OA, limited data are available for hip OA.[33] In fact, no biomarker has been found that can be used as a prognostic factor in hip OA.[33]

A study reported that, in a longitudinal dataset of patients with hip OA, five different pain trajectories could be discriminated.[28] These trajectories varied from 'highly progressive pain' to 'mild pain'. If it could be established that specific biomarkers are associated with particular trajectories, clinicians could classify patients using these biomarkers. Particularly those patients that are at high risk of progression could be monitored more closely and treated accordingly.

Patients with OA often report that their clinical symptoms are changed by weather conditions such as precipitation and temperature.[34] Moreover, about 62% of patients with OA report being weather sensitive.[35] Temperature, barometric pressure, precipitation and relative humidity have been studied in patients with OA; however, in these studies none of the meteorological variables showed a consistent correlation with patients' perceived pain in OA.[34-44] This inconsistency might be caused by differences in data collection and/or the definition of weather variables; e.g. some studies used multiple data per day, whereas others averaged the data over 24 hours.[35, 36, 41]

Hip OA and comorbidities

Another factor possibly influencing clinical symptoms in hip OA is the greater trochanter pain syndrome (GTPS). GTPS is a common tendinitis and/or bursitis in the hip region with an

incidence in general practice of 1.8 patients per 1000 per year.[45] It is defined as a tendinitis of the insertion of the gluteus medius or minimus muscle, or a trochanteric bursitis, or a combination of both.[46, 47] About 30% of patients with GTPS have concurrent low-back pain or hip OA.[48] In patients with hip OA the prevalence of GTPS is unknown, and it is also unknown whether the presence of GTPS influences the perceived pain in these patients.

Non-operative treatment

Because disease-modifying options for OA are still lacking, this has resulted in symptomatic treatment.[49] Non-operative treatment for hip OA consists of non-pharmacological and pharmacological therapies. Both focus on pain relief, maintenance of function in daily activities, and improving quality of life. If non-operative treatment fails, a total joint replacement can be considered; however, this is a costly operation with an intensive period of rehabilitation.

International guidelines advise to begin treatment with non-pharmacological management such as education, exercise and weight loss, and assistive devices.[50] These therapies can be combined with pain medication. In symptomatic OA, the first step as a first-line therapy is use of acetaminophen. Although this analgesic has few adverse reactions, it also has a small effect size (0.14) regarding pain reduction.[51] The following step is use of a non-steroidal anti-inflammatory agent; this type of analgesic has a small-to-moderate effect size for pain reduction (0.29) but is known for its adverse drug reaction, particularly gastrointestinal problems.[51] As a third step, opioids such as tramadol are advised.[50, 51]

When patients suffer pain despite these oral analgesics, several national and international guidelines recommend intra-articular corticosteroid injections for individuals with knee and hip OA.[50-52] In knee OA the effect of corticosteroid injections on pain reduction has been studied extensively. A Cochrane review of 27 trials with 1,767 participants showed moderate effect at 1-2 weeks (effect size 0.48) and small-to-moderate effect at 4-6 weeks (effect size 0.41). The quality of this evidence was graded as low because most of the trials had a high (or unclear) risk of bias.[53] Regarding hip OA, 5 randomized controlled trials on this subject were published.[54-58] A recent systematic review on the efficacy of intra-articular steroids in hip OA included these 5 randomized controlled trials and the quality of these studies was judged to be high.[59] The treatment effect was strong at one-week post-injection, but declined thereafter. At the 8-week follow-up, only two trials reported a reduction in pain (with moderate effect size).[59]

Injection into the hip joint is challenging, as the joint cannot be palpated and is adjacent to important neurovascular structures. An intra-articular hip injection is best performed under fluoroscopic or ultrasound guidance. Moreover, an intra-articular injection can lead to septic

arthritis and may increase the risk of prosthesis infection when shortly followed by total hip replacement.[60]

The systemic effect of corticosteroids had been indicated in a double-blind randomized controlled trial in patients with impingement shoulder pain.[61] A clinically relevant effect of an intramuscular corticosteroid injection might offer a less complex alternative treatment for patients with episodes of increased pain in hip OA.

Aims and contents of this thesis

This thesis focuses on diagnosing hip OA, the non-interventional factors associated with influencing the symptoms of hip OA, and the treatment effects of an intramuscular corticosteroid injection in patients with hip OA.

Chapter 2 presents the study protocol of our randomized controlled trial on the effectiveness of an intramuscular corticosteroid injection versus a placebo injection on hip pain in patients with hip OA from general practices and orthopaedic outpatient clinics. **Chapter 3** presents and discusses the results of that trial.

Chapter 4 describes a systematic review on the usefulness of an anesthetic hip joint injection in diagnosing hip OA.

Chapter 5 reports on the associations between biochemical cartilage markers and clinical symptoms over a two-year period in patients with hip OA.

To gain further insight into the influence of weather conditions on clinical symptoms in hip OA a review was performed and is reported in **Chapter 6**. This chapter also describes the associations between weather conditions and clinical symptoms in patients with hip OA in a cohort study with a two-year follow-up.

Chapter 7 describes the prevalence of greater trochanter pain syndrome in patients with hip OA, as well as the influence of this syndrome on patients' perceived hip pain.

Chapter 8 discusses the main findings, addresses the study limitations, and considers various implications for daily practice and future research.

References

1. Gommer A, Poos M. http://www.volksgezondheidenzorg.info/onderwerp/artrose/cijfers-context/incidentie-en-prevalentie - node-aantal-personen-met-artrose-bij-de-huisarts. Bilthoven: RIVM 2015.
2. Gommer A, Poos M. http://www.volksgezondheidenzorg.info/onderwerp/artrose/cijfers-context/incidentie-en-prevalentie - node-soorten-artrose. Bilthoven: RIVM 2015.
3. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis 2014; 73: 1323-1330.
4. Poos M, Gommer A. http://www.volksgezondheidenzorg.info/onderwerp/artrose/cijfers-context/trends-en-toekomst - node-trend-aantal-mensen-met-artrose. Bilthoven: RIVM 2015.
5. van der Noordt M, Poos M, Slobbe L. http://www.volksgezondheidenzorg.info/onderwerp/artrose/kosten/kosten - node-kosten-van-zorg-voor-artrose. Bilthoven: RIVM 2015.
6. Poos M, Gommer A. http://www.volksgezondheidenzorg.info/onderwerp/artrose/cijfers-context/trends-en-toekomst - node-toekomstverwachting-0. Bilthoven: RIVM 2015.
7. Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am 2008; 34: 531-559.
8. Dutch Orthopaedic Association. Guideline diagnostics and treatment of hip osteoarthritis and knee osteoarthritis. Nijmegen 2007.
9. Paans N, van der Veen WJ, van der Meer K, Bulstra SK, van den Akker-Scheek I, Stevens M. Time spent in primary care for hip osteoarthritis patients once the diagnosis is set: a prospective observational study. BMC Fam Pract 2011; 12: 48.
10. Dutch Arthroplasty Register. LROI, annual report 2014. 's Hertogenbosch 2016.
11. National Institute for Health and Care Excellence. Osteoarthritis: care and management in: http://www.nice.org.uk/guidance/cg177. Osteoarthritis: care and management 2014.
12. Lane NE, Hochberg MC, Nevitt MC, Simon LS, Nelson AE, Doherty M, et al. OARSI Clinical Trials Recommendations: Design and conduct of clinical trials for hip osteoarthritis. Osteoarthritis Cartilage 2015; 23: 761-771.
13. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.
14. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007; 15 Suppl A: A1-56.
15. 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. Rheum 2005; 44: 337-341.
16. Kim C, Nevitt MC, Niu J, Clancy MM, Lane NE, Link TM, et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. BMJ 2015; 351: h5983.
17. Reijman M, Hazes JM, Pols HA, Bernsen RM, Koes BW, Bierma-Zeinstra SM. Validity and reliability of three definitions of hip osteoarthritis: cross sectional and longitudinal approach. Ann Rheum Dis 2004; 63: 1427-1433.
18. Brown MD, Gomez-Marin O, Brookfield KF, Li PS. Differential diagnosis of hip disease versus spine disease. Clin Orthop Relat Res 2004: 280-284.
19. Crawford RW, Gie GA, Ling RS, Murray DW. Diagnostic value of intra-articular anaesthetic in primary osteoarthritis of the hip. J Bone Joint Surg Br 1998; 80: 279-281.

20. Faraj AA, Kumaraguru P, Kosygan K. Intra-articular bupivacaine hip injection in differentiation of coxarthrosis from referred thigh pain: a 10 year study. Acta Orthop Belg 2003; 69: 518-521.
21. Illgen RL, 2nd, Honkamp NJ, Weisman MH, Hagenauer ME, Heiner JP, Anderson PA. The diagnostic and predictive value of hip anesthetic arthrograms in selected patients before total hip arthroplasty. J Arthroplasty 2006; 21: 724-730.
22. Kleiner JB, Thorne RP, Curd JG. The value of bupivicaine hip injection in the differentiation of coxarthrosis from lower extremity neuropathy. J Rheumatol 1991; 18: 422-427.
23. Ashok N, Sivan M, Tafazal S. The diagnostic value of anaesthetic hip injection in differentiating between hip and spinal pain. Eur J Orhop Surg Traumatol 2009: 167-171.
24. Odoom JE, Allen GM, Wilson DJ. Response to local anaesthetic injection as a predictor of successful hip surgery. Clin Radiol 1999; 54: 430-433.
25. Pateder DB, Hungerford MW. Use of fluoroscopically guided intra-articular hip injection in differentiating the pain source in concomitant hip and lumbar spine arthritis. Am J Orthop 2007; 36: 591-593.
26. Poiraudeau S, Martinez M, Anract P, Chevrot A, Revel M. Value of hip anesthesia to characterize the main origin of pain in hip-spine osteoarthritis. Europa Medicophysica 2000; 36: 61-66.
27. Yoong P, Guirguis R, Darrah R, Wijeratna M, Porteous MJ. Evaluation of ultrasound-guided diagnostic local anaesthetic hip joint injection for osteoarthritis. Skeletal Radiol 2012; 41: 981-985.
28. Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis 2012; 71: 1517-1523.
29. Leffondre K, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. J Clin Epidemiol 2004; 57: 1049-1062.
30. Moskowitz RW, Sunshine A, Hooper M, Olson NZ, Cawkwell GD. An analgesic model for assessment of acute pain response in osteoarthritis of the knee. Osteoarthritis Cartilage 2006; 14: 1111-1118.
31. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharm & Ther 2001; 69.
32. Rousseau J, Garnero P. Biological markers in osteoarthritis. Bone 2012; 51: 265-277.
33. Hosnijeh FS, Runhaar J, van Meurs JB, Bierma-Zeinstra SM. Biomarkers for osteoarthritis: Can they be used for risk assessment? A systematic review. Maturitas 2015; 82: 36-49.
34. Laborde JM, Dando WA, Powers MJ. Influence of weather on osteoarthritics. Soc Sci Med 1986; 23: 549-554.
35. Sibley JT. Weather and arthritis symptoms. J Rheumatol 1985; 12: 707-710.
36. Aikman H. The association between arthritis and the weather. Int J Biometeorol 1997; 40: 192-199.
37. Brennan SA, Harney T, Queally JM, O'Connor McGoona J, Gormley IC, Shannon FJ. Influence of weather variables on pain severity in end-stage osteoarthritis. Int Orthop 2012; 36: 643-646.
38. Cay HF, Sezer I, Firat MZ, Kacar C. Which is the dominant factor for perception of rheumatic pain: meteorology or psychology? Rheumatol Int 2011; 31: 377-385.
39. Clarke AM, Nicholl J. Does the weather affect the osteoarthritic patient? Br J Rheumatol 1991; 30: 477.
40. Guedj D, Weinberger A. Effect of weather conditions on rheumatic patients. Ann Rheum Dis 1990; 49: 158-159.

41. McAlindon T, Formica M, Schmid CH, Fletcher J. Changes in barometric pressure and ambient temperature influence osteoarthritis pain. Am J Med 2007; 120: 429-434.
42. Strusberg I, Mendelberg RC, Serra HA, Strusberg AM. Influence of weather conditions on rheumatic pain. J Rheumatol 2002; 29: 335-338.
43. Verges J, Montell E, Tomas E, Cumelles G, Castaneda G, Marti N, et al. Weather conditions can influence rheumatic diseases. Proc West Pharmacol Soc 2004; 47: 134-136.
44. Wilder FV, Hall BJ, Barrett JP. Osteoarthritis pain and weather. Rheumatology 2003; 42: 955-958.
45. Lievense A, Bierma-Zeinstra S, Schouten B, Bohnen A, Verhaar J, Koes B. Prognosis of trochanteric pain in primary care. Br J Gen Pract 2005; 55: 199-204.
46. Fearon AM, Scarvell JM, Cook JL, Neeman T, Cormick W, Smith PN. Greater trochanteric pain syndrome: defining the syndrome. Br J Sports Med 2013; 47: e2.
47. Karpinski MR, Piggott H. Greater trochanteric pain syndrome. A report of 15 cases. J Bone Joint Surg Br 1985; 67: 762-763.
48. Brinks A, van Rijn RM, Willemsen SP, Bohnen AM, Verhaar JA, Koes BW, et al. Corticosteroid injections for greater trochanteric pain syndrome: a randomized controlled trial in primary care. Ann Fam Med 2011; 9: 226-234.
49. Tonge DP, Pearson MJ, Jones SW. The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics. Osteoarthritis Cartilage 2014; 22: 609-621.
50. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014; 43: 701-712.
51. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, 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 2010; 18: 476-499.
52. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007; 15: 981-1000.
53. Juni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015; 10: CD005328.
54. Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis 2011; 70: 110-116.
55. Flanagan J, Casale FF, Thomas TL, Desai KB. Intra-articular injection for pain relief in patients awaiting hip replacement. Ann R Coll Surg Engl 1988; 70: 156-157.
56. Kullenberg B, Runesson R, Tuvhag R, Olsson C, Resch S. Intraarticular corticosteroid injection: pain relief in osteoarthritis of the hip? J Rheumatol 2004; 31: 2265-2268.
57. Lambert RG, Hutchings EJ, Grace MG, Jhangri GS, Conner-Spady B, Maksymowych WP. Steroid injection for osteoarthritis of the hip: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2007; 56: 2278-2287.
58. Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage 2006; 14: 163-170.
59. McCabe PS, Maricar N, Parkes MJ, Felson DT, O'Neill TW. The efficacy of intra-articular steroids in hip osteoarthritis: A systematic review. Osteoarthritis Cartilage 2016.

60. Ravi B, Escott BG, Wasserstein D, Croxford R, Hollands S, Paterson JM, et al. Intraarticular hip injection and early revision surgery following total hip arthroplasty: a retrospective cohort study. Arthritis & rheumatology 2015; 67: 162-168.
61. Ekeberg OM, Bautz-Holter E, Tveita EK, Juel NG, Kvalheim S, Brox JI. Subacromial ultrasound guided or systemic steroid injection for rotator cuff disease: randomised double blind study. BMJ 2009; 338: a3112.

CHAPTER 2

Effectiveness of intramuscular corticosteroid injection versus placebo injection in patients with hip osteoarthritis: design of a randomized double-blinded controlled trial

DMJ Dorleijn, PAJ Luijsterburg, M Reijman, M Kloppenburg, JAN Verhaar, PJE Bindels, PK Bos, SMA Bierma-Zeinstra

BMC Musculoskeletal Disorders 2011, 12:280

Abstract

Background: Recent international guidelines recommend intra-articular corticosteroid injections for patients with hip osteoarthritis who have moderate to severe pain and do not respond satisfactorily to oral analgesic/anti-inflammatory agents. Of the five available randomized controlled trials, four showed positive effects with respect to pain reduction. However, intra-articular injection in the hip is complex because the joint is adjacent to important neurovascular structures and cannot be palpated. Therefore fluoroscopic or ultrasound guidance is needed. The systemic effect of corticosteroids has been studied in patients with impingement shoulder pain. Gluteal corticosteroid injection was almost as effective as ultrasound-guided subacromial corticosteroid injection. Such a clinically relevant effect of a systemic corticosteroid injection offers a less complex alternative for treatment of patients with hip osteoarthritis not responsive to oral pain medication.

Methods/Design: This is a double-blinded, randomized controlled trial. A total of 135 patients (aged > 40 years) with hip osteoarthritis and persistent pain despite oral analgesics visiting a general practitioner or orthopaedic surgeon will be included. They will be randomized to a gluteal intramuscular corticosteroid injection or a gluteal intramuscular placebo (saline) injection. The randomization will be stratified for setting (general practitioner and outpatient clinics of department of orthopaedics). Treatment effect will be evaluated by questionnaires at 2, 4, 6, and 12 weeks follow-up and a physical examination at 12 weeks. Primary outcome is severity of hip pain reported by the patients at 2-week follow-up. Statistical analyses will be based on the intention-to-treat principle.

Discussion: This study will evaluate the effectiveness of an intramuscular corticosteroid injection on pain in patients with hip osteoarthritis.

Trial Registration: This trial is registered in the Dutch Trial Registry: number NTR2966.

Background

Recent international guidelines recommend intra-articular (IA) corticosteroid injections for patients with hip osteoarthritis (OA) who have moderate to severe pain and no satisfactory response to oral analgesic/anti-inflammatory agents.[1] Of the five randomized controlled trials (RCTs) on this subject [2-6], four showed clinically significant positive effects with respect to pain reduction (effect size up to 1.5 at 1 week follow-up) [2, 4-6] and one showed no clinical benefit of an IA injection.[3] In the RCT that showed no clinical benefit of an IA injection, patients were biased towards a negative result having been informed they would receive priority for surgery if their pain worsened after injection.[3]

Because the hip joint is adjacent to important neurovascular structures and cannot be palpated, IA injection under fluoroscopic or ultrasound guidance is advised. However, these techniques are not always available, especially in a primary care setting. Moreover, apart from being complex, an IA hip injection can be painful for the patient and can lead to septic arthritis. An effective but simpler administration technique would be a welcome addition to the current methods to treat episodes of increased pain in hip OA.

A double-blind RCT in patients with subacromial impingement shoulder pain showed almost equal effectiveness of ultrasound-guided subacromial corticosteroid injection compared to gluteal (systemic) injection[7]; this effect was also reported in an earlier study.[8] In addition, an equal or even more pronounced pain decrease was found in patients with concurrent hip OA or chronic low back pain in an RCT assessing the effectiveness of a local corticosteroid injection in patients with greater trochanteric pain syndrome.[9, 10] These results indicate a systemic effect of corticosteroids on pain in OA.

A clinically relevant effect of a systemic corticosteroid injection, offers a less complex alternative for treatment of patients with hip OA who are not responsive to oral pain medication. Since IA hip injection is not standard care in the Netherlands, we decided to conduct a trial comparing intramuscular (IM) corticosteroid injection versus IM placebo injection.

Primary objective

This RCT will assess the effectiveness of an IM gluteal corticosteroid injection versus an IM gluteal placebo injection for pain in patients with hip OA who have moderate to severe pain and no satisfactory response to oral analgesic/anti-inflammatory agents during 12-weeks follow-up.

Secondary objectives

The study will assess the effectiveness of an IM gluteal corticosteroid injection versus an IM gluteal placebo injection in patients with hip OA with regard to function, mobility and patients' perceived improvement. Adverse reactions will be registered and an explorative subgroup analysis will be performed stratified for setting (general practitioner and outpatient clinics of department of orthopaedics).

Methods

Design

This is a double-blinded RCT. The Medical Ethics Committee of the Erasmus University Medical Center approved the trial (MEC2011-115). All patients will provide written informed consent.

Patient selection

Patients with hip OA will be recruited in primary care (general practices in the Rotterdam area) and via hospital referrals (orthopaedic outpatient clinics in the Rotterdam area). Treating physicians are asked to select patients with hip OA and screen them on the inclusion/exclusion criteria (Table 1). If a patient has bilateral hip OA, the most painful hip will be selected as the study hip.

Procedures

Eligible patients will receive written study information from their treating physician. If they show interest, the physician will fax their contact data to the research team. The researcher will contact the patient to answer additional questions. If the patient is interested/willing to participate, an appointment at the research centre will be made to sign an informed consent form and screen on inclusion/exclusion criteria, including assessment of radiologic hip OA. Pelvic anteroposterior (AP) X-rays taken within 6 months prior to enrolment are accepted; otherwise an AP pelvic X-ray will be taken. Two researchers will independently of each other assess grading of hip OA according to Kellgren-Lawrence (KL).[11] If the patient meets the radiologic criteria for participation (KL score of ≥ 2), baseline measurement (questionnaire and physical examination) follows.

Randomisation

An independent pharmacy assistant will allocate each patient based on computerized randomization lists to either receive placebo (saline) injection or triamcinolone acetate 40 mg injection IM. Randomization is stratified for setting (general practitioner and outpatient clinics of department of orthopaedics) and uses random blocks of 2 and 4.

Blinding

To assure blinding with respect to the patient, researcher and treating physician, the trial medication will be packed and sealed by the pharmacy of the Erasmus MC, Rotterdam. An independent research assistant (who is not otherwise involved in the study) will prepare and administer, out of sight of the patient, the injection in the upper lateral quadrant of the gluteal musculature. The injection will be administered in the gluteal area ipsilateral of the study hip.

Table 1 Patients' eligibility criteria.

Inclusion criteria
1. Hip OA* according to clinical ACR** criteria
2. Age > 40 years
3. Symptomatic disease for at least six months prior to enrolment
4. Radiographic evidence of OA* (Kellgren-Lawrence score ≥ 2)
5. Persistent pain despite receiving optimal doses of oral pain medication for at least 3 weeks. Pain severity (in rest or on walking) defined as ≥ 3 on an NRS[#] (0-10 range, 0=no pain)
Exclusion criteria
1. Inability to understand Dutch questionnaires
2. Systemic infection
3. Local infection
4. Systemic arthritis
5. Diabetes mellitus
6. Coagulopathy
7. Gastric ulcer
8. Current use of oral corticosteroids, DMARDs[$] or immunosuppressive medication
9. Allergy to corticosteroids
10. Anticoagulant therapy (coumarins)
11. On the waiting list for total hip replacement surgery
12. IA[##] injection into the hip in the previous 6 months
13. Radiologic signs of osteonecrosis
14. Participation in other medical trial
15. Pregnancy or lactating female

* OA = Osteoarthritis; **ACR = American College of Rheumatology; [#] NRS = Numerical Rating Scale; $ DMARD = disease-modifying antirheumatic drugs; [##] IA = intra-articular

Intervention

Patients who participate in the trial are randomized to either an IM triamcinolone acetate 40 mg injection once or an IM saline injection once. Patients are allowed to continue their usual pain medication or physical therapy, but are requested not to start any new therapies regarding their hip OA during study follow-up.

Outcomes

Questionnaires at baseline, 2, 4, 6 and 12 weeks

All outcomes are measured at baseline and at 2, 4, 6 and 12 weeks follow-up. The primary outcome is severity of hip pain reported by the patient at 2 weeks. This will be measured with two validated questionnaires: an 11-point numerical rating scale (NRS) in rest and on

walking (0-10, where 0 equals no pain),[12] and the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) pain subscale.[13] The WOMAC pain subscale will be converted to a 0-100 score, where 0 equals no symptoms. The WOMAC is recommended by the Osteoarthritis Research Society for use in clinical trials in patients with hip OA to measure pain and disability.[13]

Secondary outcomes include the primary outcomes at 4, 6, and 12 weeks follow-up. Additional secondary outcomes are the disease-specific WOMAC function and stiffness subscales.[13] Both the function and stiffness subscale of the WOMAC will be converted to a 0-100 score. Data on pain and function will also be obtained with the Hip disability and Osteoarthritis Outcome Score (HOOS),[14] which was developed as an extended version of the WOMAC to evaluate the whole domain of patient-relevant outcome in young and active patients and is validated in the Dutch language.[15]

For patients' perceived recovery a 7-point Likert scale will be used (score range 1 = 'worse than ever' to 7 = 'major improvement').[9, 10] Quality of life will be measured with the Euroqol (EQ-5D).[16] Constant and intermittent pain will be obtained with the questionnaire Intermittent and Constant Osteoarthritis Pain (ICOAP) taking into account both pain intensity and impact on quality of life.[17] Patients' medical consumption will be registered and adverse reactions noted.[9, 10] For this, a questionnaire will be used that covers the known local and systemic adverse reactions to corticosteroids. Data on daily pain and pain medication use will be obtained with a diary during the first 2-weeks follow-up.

Another secondary outcome is the difference in percentage of responders as defined by the OMERACT-OARSI (improvement in at least 2 of the 3 following domains: ≥20% improvement in WOMAC pain, ≥20% improvement in WOMAC function, or markedly improved on the patients' global assessment).[16]

At baseline various patient characteristics (gender, age, height, weight, race, education, marital status, occupational situation and co-morbidities) are recorded. Table 2 presents an overview of the parameters measured during follow-up.

Physical examination at baseline and 12-weeks follow-up

Both hip joints will be examined for presence of groin pain or peri-trochanteric pain at palpation, range of motion and pain at/during movement for flexion/extension, abduction, and for internal/external rotation. Hip rotations will be examined in sitting position with the hips and knees in 90°. Hip flexion/extension and abduction will be examined in supine position. A goniometer will be used to measure degrees of range of motion.[18]

To gain insight in knee and lumbar spine co-morbidity both knee joints and lumbar spine will be examined. Pain at palpation of the medial or lateral joint space of the knee, hydrops, and range of motion of flexion/extension of the knee will be registered. Pain at palpation of the spinous processes or sacro-iliac joints and lateroflexion and flexion of the lower spine (fingertip-floor distance and classic Schober test) will be examined.[19]

Table 2 Timing of measurements and outline of primary and secondary outcome measures.

	Baseline	Daily diary for 2 weeks	2 weeks	4 weeks	6 weeks	12 weeks
Primary outcome measures						
Pain score (WOMAC*)	x		x	x	x	x
Pain Score (NRS**)	x	x	x	x	x	x
Secondary outcome measures						
Function score (WOMAC)	x		x	x	x	x
Stiffness score (WOMAC)	x		x	x	x	x
HOOS***	x		x	x	x	x
Quality of life (EuroQol EQ-5D)	x		x	x	x	x
Constant and intermittent pain (ICOAP#)	x		x	x	x	x
Use of medication	x	x	x	x	x	x
Medical consumption	x		x	x	x	x
Adverse reactions			x	x	x	x
Perceived recovery			x	x	x	x
Others						
Demographic data	x					
Co-morbidity	x					
Physical examination hip, knee and lumbar spine	x					x
Laboratory assessment (ESR##, Hs-CRP###)	x					

* WOMAC = Western Ontario and McMaster University Osteoarthritis Index; ** NRS = Numerical Rating Score; *** HOOS = Hip disability and Osteoarthritis Outcome Score; # ICOAP = Intermittent and Constant Osteoarthritis Pain; ## ESR = Erythrocyte Sedimentation Rate; ### Hs-CRP = high sensitive C-reactive protein

Laboratory assessment

At baseline, two blood samples (9 ml) will be collected. One to measure the erythrocyte sedimentation rate, which is used for the American College of Rheumatology criteria of hip OA.[20] The other for high-sensitive C-reactive protein (hs-CRP) to gain insight in the inflammatory processes. The samples will be analyzed at the Trial Laboratory Department of the Erasmus MC.

Sample size

Data from the Qvistgaard et al. study (patients with hip OA from primary care and secondary care) were used to calculate our sample size.[6] That study showed a baseline standard devia-

tion (SD) of 20 for pain at rest and at walking (0-100 visual analogue scale; VAS). Assuming a minimal clinically relevant difference of 10 points (effect size 0.5), 64 patients per group will be needed to show a statistically significantly difference using 80% power and with a 5% alpha.

In that same study [6] the WOMAC total score (0-96) was used with an SD of 15. Standardized to a 0-100 score this SD is almost 16. Assuming an SD of 16 and an 8-point difference as clinically relevant (effect size 0.5), the same sample size is needed.

We checked these scores in a Dutch study population with hip OA, i.e. those with a K-L score of the hip ≥ 2 and a VAS pain score ≥ 30, participating in the GOAL study.[21] This showed they had a mean VAS score of 56.4 with an SD of 19.3, a mean WOMAC pain score of 51.2 with a SD of 16.4; these data are very similar to the SDs in the study of Qvistgaard et al. Therefore, in the planned trial, we will include 135 patients, anticipating only 5% loss to follow-up based on the relatively short follow-up and earlier experience with loss to follow-up.[21, 22]

Data analyses

Data analysis will be performed based on the 'intention to treat' principle.

Descriptive statistics will be used to describe patient's characteristics, items of physical examination, and the severity of radiologic hip OA.

Linear mixed models will be used for repeated measures to analyze the continuous outcome measures. Fixed effects will be time, time by therapy and the covariates we adjust for. For patients lost to follow-up, we will include all observed data in the analysis. Adjustment will be made for those baseline variables that change the effect estimate by more than 10%. Similar analyses with Generalized Estimating Equations techniques for repeated measures will be done for dichotomous outcome measures.

Subgroup analyses for setting will be analyzed by assessing interaction effects between type of intervention and setting on the primary outcomes; in addition, the estimates will be shown for both settings separately. We realize that these subgroup analyses will remain solely explorative because our sample size is not directed to powerful subgroup analyses.

References

1. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007; 15: 981-1000.
2. Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis 2011; 70: 110-116.
3. Flanagan J, Casale FF, Thomas TL, Desai KB. Intra-articular injection for pain relief in patients awaiting hip replacement. Ann R Coll Surg Engl 1988; 70: 156-157.
4. Kullenberg B, Runesson R, Tuvhag R, Olsson C, Resch S. Intraarticular corticosteroid injection: pain relief in osteoarthritis of the hip? J Rheumatol 2004; 31: 2265-2268.
5. Lambert RG, Hutchings EJ, Grace MG, Jhangri GS, Conner-Spady B, Maksymowych WP. Steroid injection for osteoarthritis of the hip: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2007; 56: 2278-2287.
6. Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage 2006; 14: 163-170.
7. Ekeberg OM, Bautz-Holter E, Tveita EK, Juel NG, Kvalheim S, Brox JI. Subacromial ultrasound guided or systemic steroid injection for rotator cuff disease: randomised double blind study. BMJ 2009; 338: a3112.
8. Valtonen EJ. Double acting betamethasone (Celestone Chronodose) in the treatment of supraspinatus tendinitis: a comparison of subacromial and gluteal single injections with placebo. J Int Med Res 1978; 6: 463-467.
9. Brinks A, van Rijn RM, Bohnen AM, Slee GL, Verhaar JA, Koes BW, et al. Effect of corticosteroid injection for trochanter pain syndrome: design of a randomised clinical trial in general practice. BMC Musculoskelet Disord 2007; 8: 95.
10. Brinks A, van Rijn RM, Willemsen SP, Bohnen AM, Verhaar JA, Koes BW, et al. Corticosteroid injections for greater trochanteric pain syndrome: a randomized controlled trial in primary care. Ann Fam Med 2011; 9: 226-234.
11. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494-502.
12. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27: 117-126.
13. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-1840.
14. Nilsdotter AK, Lohmander LS, Klassbo M, Roos EM. Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. BMC Musculoskelet Disord 2003; 4: 10.
15. de Groot IB, Reijman M, Terwee CB, Bierma-Zeinstra SM, Favejee M, Roos EM, et al. Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score. Osteoarthritis Cartilage 2007; 15: 104-109.

16. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004; 12: 389-399.
17. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008; 16: 409-414.
18. Bierma-Zeinstra SM, Bohnen AM, Ramlal R, Ridderikhoff J, Verhaar JA, Prins A. Comparison between two devices for measuring hip joint motions. Clin Rehabil 1998; 12: 497-505.
19. Perret C, Poiraudeau S, Fermanian J, Colau MM, Benhamou MA, Revel M. Validity, reliability, and responsiveness of the fingertip-to-floor test. Arch Phys Med Rehabil 2001; 82: 1566-1570.
20. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.
21. Rozendaal RM, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. Ann Intern Med 2008; 148: 268-277.
22. Rozendaal RM, Uitterlinden EJ, van Osch GJ, Garling EH, Willemsen SP, Ginai AZ, et al. Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial. Osteoarthritis Cartilage 2009; 17: 427-432.

CHAPTER 3

Intramuscular corticosteroid injection versus placebo injection in hip osteoarthritis: a 12- week blinded randomized controlled trial

DMJ Dorleijn, PAJ Luijsterburg, M Reijman,
M Kloppenburg, JAN Verhaar, PJE Bindels, PK Bos,
SMA Bierma-Zeinstra

Submitted

Abstract

Background: Guidelines recommend intra-articular corticosteroid injection in patients with painful hip osteoarthritis (OA). However, injection in the hip joint is an invasive procedure and best performed under fluoroscopic or ultrasound guidance. The efficacy of systemic corticosteroid treatment for pain reduction in hip OA is unknown.

Methods: In this randomized, double-blind, controlled trial we enrolled patients with painful hip OA scoring ≥3 on an 11-point numerical rating scale (NRS:0-10;0=no hip pain) despite the use of oral analgesics. Patients were randomized to receive either 40 mg of triamcinolone acetate or placebo with an intramuscular injection into the ipsilateral gluteus muscle. The primary outcome was severity of pain at 2-week follow-up measured with a NRS at rest and during walking, and with the WOMAC pain subscale (0-100; 0=no pain). Total follow-up was 12 weeks. Data analysis was performed based on the intention-to-treat principle using linear mixed models for repeated measurements.

Results: Of the 107 patients randomized, 106 could be analyzed (52 in the corticosteroid group, 54 in the placebo group). At 2-week follow-up, compared to the placebo injection, the intramuscular corticosteroid injection showed a significant and clinically relevant association with hip pain reduction at rest (difference -1.3, 95% CI -2.3 to -0.3). Moreover, the effect of the corticosteroid injection persisted for the primary outcome measures during the entire 12-week follow-up.

Conclusions: An intramuscular corticosteroid injection showed clinical effectiveness in patients with hip OA during 12 weeks of follow-up.

Funding: Financial support was received from the Dutch Arthritis Foundation and the NutsOhra Fund.

Dutch Trial Registry: NTR2966.

Introduction

Several international guidelines recommend intra-articular (IA) corticosteroid injections for patients with hip osteoarthritis (OA) experiencing moderate to severe pain and not responding to oral analgesics.[1-3] A systematic review on the efficacy of intra-articular steroids in hip osteoarthritis included 5 randomized controlled trials (RCT) and assessed quality of the studies was high.[4] The treatment effect was large at one week post-injection, but declined afterwards. At 8 weeks there were 2 trials that reported a reduction in pain (moderate effect size).[4]

However, injection into the hip joint is challenging because the joint cannot be palpated and is adjacent to important neurovascular structures. An IA hip injection is best performed under fluoroscopic or ultrasound guidance. Moreover, an IA injection can lead to a septic arthritis[5], and an IA corticosteroid injection may increase the risk of prosthesis infection when shortly followed by total hip replacement (THR).[6]

A systemic effect of corticosteroids on joint pain has been indicated in patients with subacromial impingement shoulder pain. A double-blinded RCT showed no important differences in effectiveness on pain of ultrasound-guided subacromial corticosteroid injection compared to gluteal injection.[7] A systemic effect of corticosteroids was also suggested in an RCT reporting the effect of local corticosteroid injection for greater trochanteric pain syndrome: patients with concurrent hip OA or chronic low back pain had an equal or even more pronounced decrease in pain.[6, 8]

If an intramuscular (IM) corticosteroid injection is shown to have a clinically relevant effect on pain, this would offer a less complex alternative treatment for episodes of increased pain in hip OA. Therefore, this study assessed the efficacy of an IM corticosteroid injection compared to an IM placebo injection on hip pain severity in patients with hip OA who were not responding to oral analgesics.

Methods

Trial design

This was a multicenter, double-blinded, randomized controlled superiority trial with two parallel groups and a follow-up period of 12 weeks: details of the study protocol are already published.[9] The Medical Ethics Committee of the Erasmus University Medical Center (EMC; Rotterdam) approved the study protocol (MEC2011-115) and all included patients provided written informed consent.

Patients

Patients with hip OA were invited to participate in the trial by general practitioners and orthopaedic surgeons located in the south-west of the Netherlands. Patients (aged >40 years) were eligible

for inclusion if they met the American College for Rheumatology (ACR) clinical criteria for hip OA during clinical screening and radiologic evidence of hip OA was present [Kellgren & Lawrence score (KL) ≥2].[10, 11] Patients were included if they had symptomatic disease for ≥6 months, and had a pain score ≥3 (scale 0-10; 0=no pain) despite the use of oral analgesics at time of inclusion.

Radiologic hip OA was scored on an anterior-posterior pelvic radiograph of (at most) 6 months old. The radiologic grade of hip OA was scored by two researchers (DD, PKB) independently and the inter-observer reliability was κ=0.7 for KL<2 versus KL≥2. In case of disagreement a consensus was formed during a consensus meeting. If a patient had bilateral hip OA, the most painful hip was selected as the study hip.

Patients were excluded if they had diabetes mellitus, were using oral corticosteroids, had local/systemic infection, had presence of inflammatory rheumatic diseases (e.g. rheumatoid arthritis, psoriatica arthritis, spondylartropathies), coagulopathy, use of coumarins, had a gastric ulcer, allergy to corticosteroids, radiologic signs of osteonecrosis, had an IA injection in the hip in the previous 6 months, were on the waiting list for THR surgery, or were unable to complete questionnaires in Dutch.

Interventions

Patients received either 40 mg triamcinolone acetate or 40 mg saline (placebo) with an IM injection. At the research center the trial nurse administered the allocated injection in the upper lateral quadrant of the gluteal musculature on the ipsilateral side of the study hip.

Randomization

An independent pharmacy assistant allocated each included patient based on a computerized randomization list using random blocks of 2 and 4 to either placebo (saline) injection or triamcinolone acetate 40 mg injection. Randomization was stratified for setting (general practice and orthopaedic outpatient clinic). After randomization the vials for the injections were prepared, packed and sealed in an identical way for both groups by the pharmacy of the EMC. The randomization list was available only to the pharmacy assistant.

Blinding

In this trial, the outcome assessors, patients, treating physicians, researchers (including the statistical analyses) and research assistants involved in data collection were blinded to the content of the injections. To assure blinding, the independent trial nurse not involved with follow-up measurements prepared and administered the injection out of sight of the patient, assessors, treating physicians, and the researchers. After preparation, and before injection, the syringe was covered with an opaque foil to assure blinding of the patient.

Outcomes

The primary outcome was severity of hip pain at 2 weeks, measured on an 11-point numerical rating scale (NRS: 0-10, 0=no pain) at rest and on walking, and with the Western Ontario and McMaster University Osteoarthritis Index pain subscale (WOMAC pain: 0-100, 0=no symptoms).[12, 13]

Secondary outcomes were the primary outcomes at 4, 6, and 12-week follow-up. Additional secondary outcome measures were WOMAC function and stiffness, WOMAC total score, Hip disability and Osteoarthritis Outcome Score for pain (HOOS pain), and function in daily living (HOOS ADL), quality of life (EQ-5D), Intermittent and Constant Osteoarthritis Pain (ICOAP), and patients' perceived recovery assessed on a 7-point Likert scale.[14-16] At all time points the WOMAC and ICOAP scales are presented as normalized scores (0-100, 0= no symptoms). The HOOS subscales are presented as normalized scores (0-100, 100= no symptoms). Also recorded was patients' medical consumption, including analgesic use and adverse reactions, at all time points. Patients were allowed to use escape pain medication as needed.

Another secondary outcome was the percentage of responders as defined by the OMERACT-OARSI criteria (improvement in at least 2 of the 3 following domains: ≥20% improvement in WOMAC pain, ≥20% improvement in WOMAC function, or markedly improved on patients' global assessment).[15] For patients' global assessment the 7-point Likert scale for patients' perceived recovery was dichotomized in 'improved' (scores: completely recovered, almost completely recovered, and slightly recovered) and 'not improved' (scores: no change, slightly worse, significantly worsened, and worse than ever).

At baseline and at 12-week follow-up, patients visited the research center to undergo a physical examination of hips, spine and knees by the research assistant. At baseline, blood samples were collected to measure the erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) to gain insight in the inflammatory processes. Samples were analyzed at the Trial Laboratory Department of the EMC.

Sample size

We based our power calculations on the standard deviation SDs reported for a study population with similar inclusion criteria.[17] A 10-point difference (SD 20) on the hip pain at rest and during walking [visual analogue scale (VAS): 0-100] was assumed to be the minimal clinically important difference between both groups (effect size of 0.5). With a power of 80% and an alpha of 5%, 64 patients per group were required (including 5% loss to follow-up=67 patients per group). The same sample size was needed when assuming an 8-point difference (SD 16) on the standardized WOMAC total score (0-100) as a clinically relevant difference between the groups.

Statistical analysis

Data analysis was performed based on the intention-to-treat principle. Descriptive statistics were used to describe patients' characteristics at baseline, items of physical examination, and the severity of radiologic hip OA. Linear mixed models with repeated measures were used for continuous outcomes. When patients underwent a THR, data of these patients were included up to the date of surgery. To model the covariance of repeated measures by patients, the unstructured structure was chosen, because this yielded the lowest Akaike's information criterion. Fixed effects were time, and time by treatment. Analyses were adjusted for baseline variables that changed the effect estimate by ≥10%.

Generalized estimating equations analyses (GEE) with repeated measures were performed for the dichotomous outcomes perceived improvement, and the OMERACT-OARSI responder. Before GEE analyses, multiple imputations were performed for missing values, creating five imputed datasets.

The Pearson chi^2 test was used to analyze differences between groups concerning medical consumption, analgesic use, and adverse events. An explorative, pre-defined, subgroup analysis was performed assessing the interaction effects between injections and setting (general practice and orthopaedic outpatient clinic) on the primary outcomes.[9]

All analyses were performed using SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY, USA).

Results

Patient flow

A total of 422 invited patients contacted the research center and were screened for eligibility; of these, 92 refused to participate and 223 did not meet the inclusion criteria (Figure 1). Finally, 107 patients provided informed consent: 53 were randomized to the corticosteroid injection and 54 to the placebo injection. One patient in the corticosteroid group withdrew his consent just before the appointment for baseline physical examination and subsequent injection, because his pain had resolved spontaneously. Because this patient did not receive the allocated treatment, and was not willing to send us the completed baseline questionnaire or any follow-up questionnaires, he was not included in the analyses.

Recruitment

Recruitment of patients took place between September 2011 and October 2014 and follow-up measurements were done until January 2015. Of the 107 included patients, general practitioners referred 81 patients and orthopaedic surgeons referred 26 patients.

Lost to follow-up

At 6-week follow-up one patient in the corticosteroid group reported being scheduled for a THR; in the placebo group two patients (at 4 and 6-week follow-up, respectively) reported being scheduled for a THR. One patient in the placebo group was not willing to participate after 6 weeks due to logistical problems.

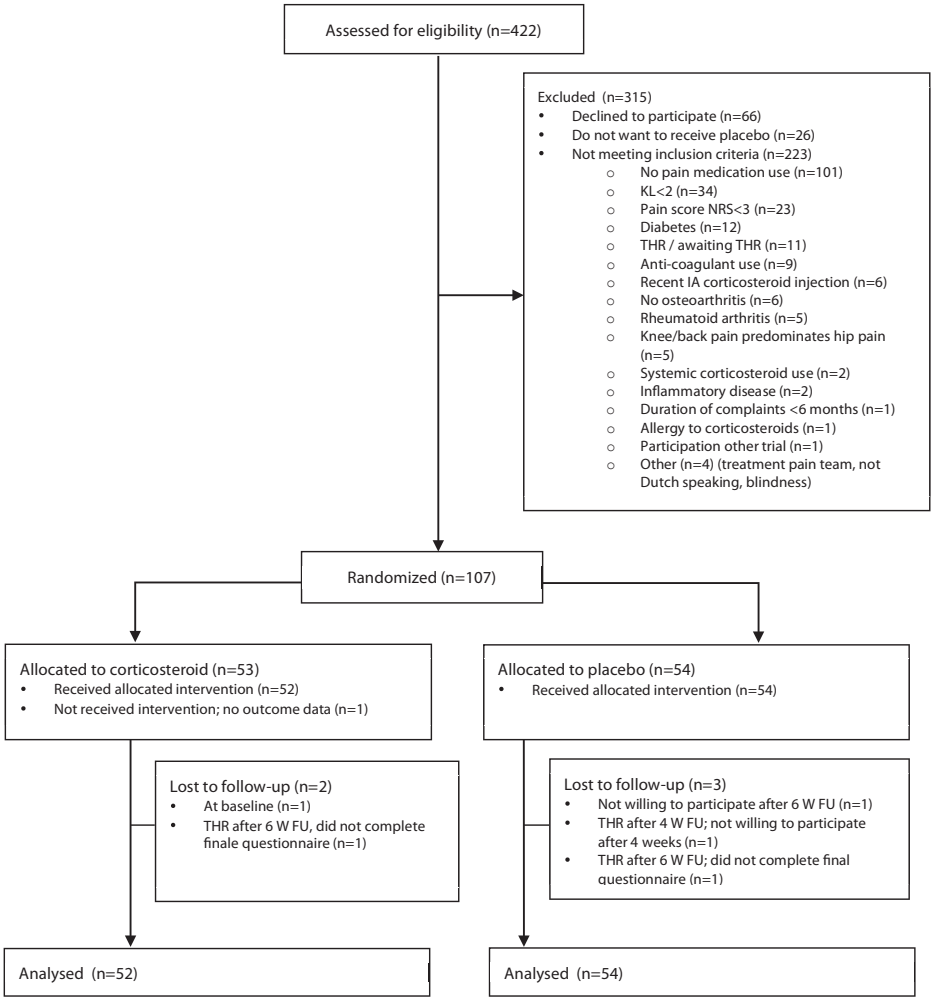


Figure 1 Flow diagram of the study participants.
NRS = numerical rating scale (0-10; 0=no pain); THR=total hip replacement; IA=intra-articular; KL=Kellgren & Lawrence score for hip osteoarthritis; W=weeks; FU=follow-up

Patient population

Of all patients, 52 received the allocated corticosteroid injection and 54 the allocated placebo injection, and were included in the analyses. Baseline characteristics of both patient groups

Table 1 Patients' characteristics at baseline.

Characteristic		Corticosteroid (n= 52)	Placebo (n = 54)
Women, n (%)		40 (77)	33 (61)
Age in years, mean (SD)		66 (11)	63 (10)
Body mass index, kg/m2, mean (SD)		27 (3.7)	28 (6.4)
Duration of symptoms, n (%)	< 1 y	12 (23)	20 (37)
	≥ 1 y	40 (77)	34 (63)
Referral to study by, n (%)	General practitioner	39 (75)	41 (76)
	Orthopedic surgeon	13 (25)	13 (24)
Kellgren & Lawrence score hip OA, n (%)	KL 2	42 (81)	38 (70)
	KL≥ 3	10 (19)	16 (30)
Ethnicity Dutch, n (%)		51 (98)	47 (87)
Employment, n (%)		17 (33)	23 (43)
Comorbidities (self reported)			
Osteoarthritis of knee(s), n (%)		20 (39)	15 (28)
Osteoarthritis of hand(s), n (%)		12 (23)	14 (26)
Low back pain, n (%)		33 (64)	30 (56)
Signs and symptoms			
Stiffness of the hip, n (%)	Morning stiffness	40 (77)	35 (65)
Severity of hip pain last week NRS 0-10, mean (SD)	Pain at rest	4.3 (2.4)	4.2 (2.5)
	Pain at walking	5.4 (2.1)	5.1 (2.3)
WOMAC 0-100, mean (SD)	Total score	46 (19)	47 (18)
	Pain	43 (17)	43 (17)
	Impairment	47 (20)	48 (19)
	Stiffness	52 (21)	48 (24)
HOOS 0-100, mean (SD)	Pain	52 (17)	52 (16)
	ADL	53 (20)	52 (19)
ICOAP 0-100, mean (SD)	Total score	38 (18)	39 (17)
	Intermittent pain	41 (21)	41 (17)
	Continuous pain	34 (21)	36 (19)
EQ5D score range, mean (SD)		0.658 (0.234)	0.682(0.264)
Treatment			
Frequent pain medication use*, n (%)	Acetaminophen	25 (48)	26 (48)
	NSAID	14 (27)	14 (26)
	Opiates	8 (15)	6 (11)
Visited healthcare giver for hip OA in the previous 3 months, n (%)	General practitioner Number of visits (median, range)	24 (46) 1 (1-5)	22 (41) 1 (1-3)
	Physiotherapist Number of visits (median, range)	14 (27) 6 (1-24)	22 (41) 5.5 (1-25)
	Medical specialist Number of visits (median, range)	16 (31) 1 (1-3)	18 (33) 1 (1-4)
Patients' expected effect of injection, n (%)	Much or very much	36 (69)	29 (54)
Laboratory outcomes			
CRP, median (range)		2 (0-11)	1.5 (0-16)
ESR, median (range)		9.5 (2-67)	10 (2-60)

SD = standard deviation; Y = years; KL = Kellgren & Lawrence grading of radiologic hip OA; NRS = numeric rating scale (0 = no pain); WOMAC = Western Ontario and McMaster University Osteoarthritis Index (0 = no pain); HOOS = Hip disability and Osteoarthritis Outcome Score (0 = extreme problems); ADL = function in daily living; ICOAP = Intermittent and Constant Osteoarthritis Pain (0 = no pain); EQ5D = Euroqol; NSAID = non-steroidal anti-inflammatory drug; OA = osteoarthritis; CRP = C-reactive protein; ESR = Erythrocyte Sedimentation Rate; * Frequent pain medication use = 3-5 times/week or daily use in the past 3 weeks

Table 2 Results of multivariable linear mixed model analysis with repeated measurements regarding primary and secondary outcomes between the corticosteroid and placebo group.

		Corticosteroid (n=52)	Placebo (n=54)	Difference * (95% CI)	p- value
Primary outcome					
NRS (rest) (0-10)	2 w	2.6 (2.3)	3.9 (2.5)	-1.3 (-2.3 to -0.3)	0.01
NRS (walking) (0-10)	2 w	3.5 (2.4)	4.2 (2.5)	-0.9 (-1.9 to 0.1)	0.07
WOMAC pain (0-100)	2 w	35 (18)	39 (17)	-6.1 (-13.4 to 1.2)	0.10
Secondary outcome					
NRS pain (rest) (0-10)	4 w	2.8 (2.1)	3.9 (2.5)	-1.2 (-2.1 to -0.2)	0.01
	6 w	2.6 (2.3)	4.0 (2.6)	-1.4 (-2.4 to -0.5)	0.005
	12 w	3.2 (2.4)	4.2 (2.8)	-1.2 (-2.3 to -0.2)	0.02
NRS pain (walking) (0-10)	4 w	3.5 (2.2)	4.5 (2.5)	-1.1 (-2.0 to -0.2)	0.01
	6 w	3.4 (2.2)	4.6 (2.5)	-1.4 (-2.3 to -0.4)	0.004
	12 w	4.0 (2.5)	5.0 (2.7)	-1.3 (-2.2 to -0.3)	0.01
WOMAC pain (0-100)	4 w	34 (19)	39 (18)	-7.0 (-14.4 to 0.4)	0.06
	6 w	32 (18)	40 (20)	-9.9 (-17.7 to -2.2)	0.01
	12 w	33 (18)	40 (23)	-9.6 (-18.0 to -1.2)	0.03
WOMAC function (0-100)	2 w	36 (20)	43 (19)	-7.6 (-15.5 to 0.4)	0.06
	4 w	36 (19)	44 (21)	-9.3 (-17.2 to -1.4)	0.02
	6 w	36 (20)	43 (21)	-8.2 (-16.5 to 0.1)	0.05
	12 w	37 (19)	44 (24)	-8.9 (-17.6 to -0.1)	0.05
WOMAC stiffness (0-100)	2 w	39 (21)	47 (21)	-9.4 (-17.2 to -1.6)	0.02
	4 w	39 (23)	48 (23)	-11.6 (-20.1 to -3.2)	0.008
	6 w	38 (23)	46 (25)	-10.9 (-20.1 to -1.7)	0.02
	12 w	39 (25)	48 (26)	-12.2 (-21.7 to -2.8)	0.01
WOMAC total (0-100)	2 w	36 (19)	42 (18)	-7.5 (-15.0 to -0.1)	0.05
	4 w	36 (18)	43 (20)	-8.9 (-16.4 to -1.4)	0.02
	6 w	35 (19)	43 (20)	-9.0 (-17.0 to -1.0)	0.03
	12 w	37 (19)	44 (24)	-9.4 (-17.8 to -0.9)	0.03
HOOS pain (0-100)	2 w	59 (19)	55 (17)	6.7 (-0.7 to 14.1)	0.08
	4 w	60 (18)	56 (17)	6.4 (-0.7 to 13.5)	0.08
	6 w	61 (18)	54 (19)	9.0 (1.6 to 16.4)	0.02
	12 w	60 (18)	54 (22)	8.7 (0.8 to 16.6)	0.03
HOOS ADL (0-100)	2 w	64 (20)	57 (19)	7.6 (-0.4 to 15.6)	0.06
	4 w	64 (19)	56 (21)	9.3 (1.4 to 17.2)	0.02
	6 w	64 (20)	57 (21)	8.2 (-0.1 to 16.5)	0.05
	12 w	63 (19)	56 (24)	8.9 (0.1 to 17.6)	0.05
ICOAP intermittent (0-100)	2 w	30 (19)	37 (20)	-8.0 (-16.0 to 0.1)	0.05
	4 w	31 (19)	40 (21)	-10.0 (-18.0 to -1.9)	0.02
	6 w	28 (20)	40 (22)	-13.1 (-21.4 to -4.7)	0.002
	12 w	30 (20)	40 (23)	-11.7 (-20.4 to -2.9)	0.009

Table 2 Results of multivariable linear mixed model analysis with repeated measurements regarding primary and secondary outcomes between the corticosteroid and placebo group. (continued)

		Corticosteroid (n=52)	Placebo (n=54)	Difference * (95% CI)	p- value
ICOAP constant (0-100)	2 w	24 (20)	32 (21)	-9.8 (-18.2 to -1.4)	0.02
	4 w	25 (20)	34 (23)	-10.4 (-19.0 to -1.8)	0.02
	6 w	23 (21)	33 (23)	-11.8 (-20.5 to -3.1)	0.008
	12 w	25 (17)	36 (25)	-12.2 (-20.7 to -3.8)	0.005
ICOAP total (0-100)	2 w	27 (18)	35 (20)	-8.8 (-16.3 to -1.3)	0.02
	4 w	28 (18)	37 (22)	-10.2 (-18.1 to -2.3)	0.01
	6 w	26 (18)	37 (22)	-12.5 (-20.5 to -4.4)	0.003
	12 w	28 (17)	38 (23)	-11.9 (-20.1 to -3.8)	0.004
quality of life EQ-5D	2 w	0.772 (0.14)	0.711 (0.21)	0.054 (-0.017 to 0.126)	0.14
	4 w	0.742 (0.20)	0.705 (0.24)	0.029 (-0.058 to 0.115)	0.51
	6 w	0.777 (0.17)	0.712 (0.20)	0.064 (-0.012 to 0.140)	0.10
	12 w	0.757 (0.18)	0.692 (0.26)	0.080 (-0.012 to 0.017)	0.09

Values in mean (SD); model adjusted for KL-score at baseline, ethnicity, morning stiffness and patients' expected effect of injection; * placebo group is reference group; SD = standard deviation; 95%CI = 95% confidence interval; WOMAC = Western Ontario and McMaster Universities Index (0 = no pain); NRS = Numerical Rating Scale (0 = no pain); HOOS = Hip disability and Osteoarthritis Outcome Score (0 = extreme problems); ICOAP = intermittent and constant osteoarthritis pain (0 = no pain); EQ-5D = Euroqol; w = weeks

are presented in Table 1. Of the 106 patients, 73 (68%) were female; mean age was 64 (SD 11) years, and the duration of hip OA symptoms was ≥1 year for 74 (70%) patients. Of all patients, 75% was referred to our study by general practitioners.

The estimates for the primary outcome were changed ≥10% by the KL score of hip OA at baseline, ethnicity, morning hip stiffness, and patients' expected effect of the injection. Patients in both groups were asked to guess the allocated treatment just after the injection was given (corticosteroid/ placebo/ don't know). Very few patients correctly guessed their allocated treatment, i.e. in the corticosteroid group 3 patients (6%) and in the placebo group 6 patients (11%). In both groups most patients claimed not to know what treatment had been given, i.e. in the corticosteroid group 46 patients (89%) and in the placebo group 40 patients (75%).

Primary outcome

At 2-week follow-up, compared to the placebo injection, the corticosteroid injection showed a significant and clinically relevant association with hip pain reduction at rest (between group difference -1.3, 95% CI -2.3 to -0.3) (Table 2). Also, at 2-week follow-up, there were no signifi-

cant associations between corticosteroid injection and hip pain during walking and WOMAC pain. The results of the unadjusted linear mixed model analysis were similar (Appendix A).

Secondary outcomes

At 4, 6 and 12-week follow-up the corticosteroid injection was associated with a significant and clinically relevant hip pain reduction at rest and during walking (Table 2). Moreover, at almost all follow-up measurements, the estimates showed significant and clinically relevant differences in favor of the corticosteroid injection on WOMAC pain, function, stiffness, and total; HOOS pain and HOOS ADL; and ICOAP total, intermittent and constant. No significant differences between groups were found for quality of life (Table 2). At 2-week follow-up, perceived improvement and the OMERACT-OARSI responders showed a significant effect in favor of corticosteroid injection: OR 2.8 (95% CI 1.3-6.4) and OR 3.0 (95% CI 1.2-7.2), respectively (Table 3).

Table 3 Results of the GEE analyses with repeated measurements regarding recovery and treatment responders between the corticosteroid and placebo group.

		Corticosteroid (n=52)	Placebo (n=54)	OR (95% CI)	p- value
Perceived improvement **	2 w	30 (58)	17 (32)	2.8 (1.3 to 6.4)	0.01
	4 w	25 (48)	15 (28)	2.3 (1.0 to 5.3)	0.05
	6 w	23 (44)	17 (32)	1.7 (0.7 to 3.8)	0.24
	12 w	22 (42)	16 (30)	1.6 (0.7 to 3.6)	0.26
Responder***	2 w	24 (46)	12 (22)	3.0 (1.3 to 7.2)	0.02
	4 w	21 (40)	15 (28)	1.7 (0.7 to 4.1)	0.23
	6 w	23 (44)	16 (30)	1.9 (0.8 to 4.5)	0.21
	12 w	22 (42)	17 (32)	1.5 (0.6 to 3.4)	0.36

Values are n (%)* analyses adjusted for KL-score at baseline, ethnicity, morning stiffness and patients expected effect of injection; ** perceived improvement indicates scores completely improved, significantly improved and slightly improved; *** according to the OMERACT-OARSI criteria; GEE= Generalized Estimating Equations; OR = odds ratio; 95%CI = 95% confidence interval; w = weeks

Adverse events and medical consumption

At 2-week follow-up, 27 adverse events were reported in the corticosteroid group versus 18 in the placebo group (Table 4). Hot flushes, headache and itching were reported most frequently in the corticosteroid group. There were no significant differences in medical consumption between the two groups (Appendix B).

Table 4 Adverse events in the two study groups at 2-week follow-up.

Adverse events* at 2 weeks	Corticosteroid (n= 52)	Placebo (n= 54)
SOC Reproductive system and breast disorders		
Hot flushes	8 (15)	4 (7)
Irregular menstruation	0	0
SOC Immune system disorders		
Itching	4 (8)	1 (2)
Urticaria	1 (2)	0
SOC Respiratory, thoracic and mediastinal disorders		
Dyspnea	0	1 (2)
Epistaxis	1 (2)	0
SOC Nervous system disorders		
Headache	5 (10)	4 (7)
Cramp	2 (4)	0
Paresthesia	0	1 (2)
Sweating	2 (4)	0
SOC Musculoskeletal and connective tissue disorder		
Pain in extremity	2 (4)	2 (4)
SOC Gastrointestinal disorders		
Bowel complaints	0	1 (2)
Nausea	0	1 (2)
SOC General disorders and administration site condition		
Pain	2 (4)	0
Fatigue	0	1 (2)
SOC Psychiatric disorders		
Agitation	0	1 (2)
Nervous	0	1 (2)

Values in n (%); SOC = system organ class; * classified according to Common Terminology Criteria for Adverse Events Version 4.0, National Institutes of Health National Cancer Institute

Ancillary analyses

In the explorative subgroup analyses, the effects of hip pain reduction in the corticosteroid group were greater for patients from orthopaedic outpatient clinics than for patients from general practices [NRS at rest at 2-week follow-up: between-group difference -2.3 (95% CI-4.4 to -0.2); between-group difference in primary care -0.9 (95% CI -2.0 to 0.2)]. However, the results of the analyses of the interaction of setting on injections showed no significant interaction differences between the two groups (NRS at rest at 2-week follow-up 1.5; 95% CI -0.6 to 3.7).

Discussion

This study shows that, at 2-week follow-up, compared to an IM placebo injection an IM corticosteroid injection is clinically effective in patients with painful hip OA with regard to hip pain reduction. Moreover, the clinical effectiveness of the IM corticosteroid injection persisted during the entire 12-week follow-up period. Also, the IM corticosteroid injection had a positive effect at almost all follow-up moments on other pain measures, function, and mobility of the hip in patients with painful hip OA.

The effect of an IA corticosteroid injection for pain reduction in hip OA has been reported in several RCTs.[17-20] The present study shows that systemic treatment with an IM corticosteroid injection is effective compared to placebo on pain reduction in patients with hip OA. There are several advantages of an IM injection compared with an IA hip injection. First, the administration is much easier without the need for ultrasound/radiologic guidance and can, therefore, be performed in both secondary and primary care.

Another advantage is that an IM injection has no known risk of septic arthritis. Although the prevalence of septic arthritis following IA corticosteroid injections is low (4.6 per 100,000 injections), the implications are far-reaching.[5] There is often a need for operative lavage and prolonged antibiotic regimes.[5]

A third advantage of IM injection compared to IA injection is a reduction in the risk of prosthesis infection following subsequent THR implantation. An IA hip injection in the year preceding THR increases the risk of prosthesis infection (3.3% versus 2.4% for patients who did not receive IA injection), leading to early revision surgery.[6]

Strengths and limitations

An important strength of our placebo RCT is that it was blinded for outcome assessors, patients, treating physicians, and researchers (including the statistical analyses); also, it was performed without financial support from any pharmaceutical company. Secondly, we had a high follow-up rate, i.e. 100% at 2 weeks in both groups, which was the primary outcome time point. At 12-week follow-up, the follow-up rate was 98% in the corticosteroid injection group and 94% in the placebo group.

A limitation is that we were unable to include our pre-calculated sample size of 128 participants. Nevertheless, the results show that, with the present sample size, we were still able to detect significant differences on the score levels of our predefined clinically relevant cutoff points.

It was surprising to see that 92 patients (22%) declined to participate after receiving additional study information, mostly because they did not want to risk receiving a placebo. Similarly, in their placebo-controlled trial with IA corticosteroid injection for hip OA, Lambert et al. found that almost 50% of their patients refused to participate to avoid the risk of being allocated to placebo treatment.[20] Secondly, although our patients reported moderate to

severe pain (NRS ≥3), the main exclusion criterion was that they had not used any analgesics during the past 3 weeks. It would be interesting to establish why patients with moderate to severe pain do not take analgesics. For hip OA little is known about patients' preference and perceptions on treatment. In knee OA, although about 75% of patients use over-the-counter oral analgesics, they do not perceive this treatment as being the most effective; instead, patients perceived viscosupplementation (74.1%), narcotics (67.8%) and steroid injection (67.6%) as being the most effective.[21]

To exclude patients with other painful hip diseases, we set strict criteria for the presence of radiologic hip OA (KL ≥2). These strict criteria led to the exclusion of 8% of the screened patients.

A final point was the exclusion of patients with diabetes mellitus, a frequently occurring comorbidity in this patient population. It is well known that glucocorticoids can give rise to hyperglycemia in diabetic patients; this effect is highest after acute administration during the second to fourth week, with remission thereafter.[22] For reasons of patient safety, our medical ethics committee stipulated that we exclude diabetic patients from the present trial; this means that we cannot extrapolate our results to patients with diabetes and hip OA.

A surprising finding was that, for patients' perceived improvement and the OMERACT-OARSI responders, there was a significant association in favor of corticosteroid injection only at 2-week follow-up. There are two possible explanations for this. First, for patients' perceived improvement we dichotomized the 7-point Likert scale, which resulted in less power. Second, the answer options we provided in the questionnaire were not clearly formulated. For example, answer options were 'completely recovered', 'almost completely recovered' and 'slightly recovered', resulting in a large step between 'almost completely recovered' and 'slightly recovered'. A better delineation would have been: 'completely improved', 'markedly improved' and 'slightly improved'.

Another finding is that pain reduction after IM corticosteroid injection was still present at a similar degree at 12-week follow-up. Previous studies on IA corticosteroid injections in hip OA studies mostly showed a peak effect after 1-3 weeks, but still showed significant pain reduction at 8-12 weeks follow-up.[17-20] In a recent Cochrane review on IA corticosteroid injections in knee OA, the effects were moderate at 1-2 weeks after treatment (effect size 0.48), small to moderate at 4-6 weeks (effect size 0.41), and small at 13 weeks after treatment (effect size 0.22).[23]

To gain insight into the inflammatory processes that might be present in hip OA, we planned to analyze high-sensitive C-reactive protein. However, we only report C-reactive protein because the Trial Laboratory stopped supporting measurement of high-sensitive CRP during the inclusion period. Nevertheless, another large cohort study (349 patients with hip OA and 2806 controls) showed no evidence for an association between serum C-reactive protein and incidence or progression of OA.[24]

In our RCT we gave a single IM corticosteroid injection. In clinical practice, patients are sometimes offered multiple IA injections per year. However, there are concerns that even one IA corticosteroid injection may cause toxicity to chondrocytes, possibly resulting in progression of OA. This has been confirmed in in-vitro and in-vivo animal studies and needs further study in humans.[25, 26] It is unknown whether a single IM corticosteroid injection has a negative effect on chondrocytes.

Intramuscular corticosteroid injection showed to be an additional conservative treatment option to reduce hip pain in patients with painful hip OA. However, because it is unknown whether IM corticosteroid injection can effectively replace IA corticosteroid injection, more investigation is required. Also, future research should explore the possible negative effects on chondrocytes in corticosteroid treatment,[25, 26] and the effectiveness of IM injection in knee OA.

Based on the present results we conclude that an IM corticosteroid injection, compared to IM placebo, shows clinical effectiveness in patients with hip OA for at least 12 weeks follow-up.

References

1. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014; 43: 701-712.
2. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007; 15: 981-1000.
3. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, 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 2010; 18: 476-499.
4. McCabe PS, Maricar N, Parkes MJ, Felson DT, O'Neill TW. The efficacy of intra-articular steroids in hip osteoarthritis: A systematic review. Osteoarthritis Cartilage 2016.
5. Pal B, Morris J. Perceived risks of joint infection following intra-articular corticosteroid injections: a survey of rheumatologists. Clinical rheumatology 1999; 18: 264-265.
6. Ravi B, Escott BG, Wasserstein D, Croxford R, Hollands S, Paterson JM, et al. Intraarticular hip injection and early revision surgery following total hip arthroplasty: a retrospective cohort study. Arthritis & rheumatology 2015; 67: 162-168.
7. Ekeberg OM, Bautz-Holter E, Tveita EK, Juel NG, Kvalheim S, Brox JI. Subacromial ultrasound guided or systemic steroid injection for rotator cuff disease: randomised double blind study. BMJ 2009; 338: a3112.
8. Brinks A, van Rijn RM, Willemsen SP, Bohnen AM, Verhaar JA, Koes BW, et al. Corticosteroid injections for greater trochanteric pain syndrome: a randomized controlled trial in primary care. Ann Fam Med 2011; 9: 226-234.
9. Dorleijn DM, Luijsterburg PA, Reijman M, Kloppenburg M, Verhaar JA, Bindels PJ, et al. Effectiveness of intramuscular corticosteroid injection versus placebo injection in patients with hip osteoarthritis: design of a randomized double-blinded controlled trial. BMC Musculoskelet Disord 2011; 12: 280.
10. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.
11. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494-502.
12. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-1840.
13. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986; 27: 117-126.
14. Brooks R. EuroQol: the current state of play. Health Policy 1996; 37: 53-72.
15. Hawker GA, Davis AM, French MR, Cibere J, Jordan JM, March L, et al. Development and preliminary psychometric testing of a new OA pain measure--an OARSI/OMERACT initiative. Osteoarthritis Cartilage 2008; 16: 409-414.

16. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004; 12: 389-399.
17. Qvistgaard E, Christensen R, Torp-Pedersen S, Bliddal H. Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline. Osteoarthritis Cartilage 2006; 14: 163-170.
18. Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis 2011; 70: 110-116.
19. Kullenberg B, Runesson R, Tuvhag R, Olsson C, Resch S. Intraarticular corticosteroid injection: pain relief in osteoarthritis of the hip? J Rheumatol 2004; 31: 2265-2268.
20. Lambert RG, Hutchings EJ, Grace MG, Jhangri GS, Conner-Spady B, Maksymowych WP. Steroid injection for osteoarthritis of the hip: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2007; 56: 2278-2287.
21. Posnett J, Dixit S, Oppenheimer B, Kili S, Mehin N. Patient preference and willingness to pay for knee osteoarthritis treatments. Patient preference and adherence 2015; 9: 733-744.
22. Tamez-Perez HE, Quintanilla-Flores DL, Rodriguez-Gutierrez R, Gonzalez-Gonzalez JG, Tamez-Pena AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. World journal of diabetes 2015; 6: 1073-1081.
23. Juni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015; 10: CD005328.
24. Kerkhof HJ, Bierma-Zeinstra SM, Castano-Betancourt MC, de Maat MP, Hofman A, Pols HA, et al. Serum C reactive protein levels and genetic variation in the CRP gene are not associated with the prevalence, incidence or progression of osteoarthritis independent of body mass index. Annals of the rheumatic diseases 2010; 69: 1976-1982.
25. Sherman SL, James C, Stoker AM, Cook CR, Khazai RS, Flood DL, et al. In Vivo Toxicity of Local Anesthetics and Corticosteroids on Chondrocyte and Synoviocyte Viability and Metabolism. Cartilage 2015; 6: 106-112.
26. Sherman SL, Khazai RS, James CH, Stoker AM, Flood DL, Cook JL. In Vitro Toxicity of Local Anesthetics and Corticosteroids on Chondrocyte and Synoviocyte Viability and Metabolism. Cartilage 2015; 6: 233-240.

Appendix A Unadjusted results of the multivariable linear mixed model analysis with repeated measurements regarding primary and secondary outcomes between the corticosteroid and placebo group.

		Difference * (95% CI)	p- value
Primary outcome			
NRS (rest) (0-10)	2 w	-1.3 (-2.2 to -0.3)	0.008
NRS (walking) (0-10)	2 w	-0.8 (-1.7 to 0.2)	0.11
WOMAC (0-100)	2 w	-4.6 (-11.4 to 2.2)	0.18
Secondary outcome			
NRS pain (rest) (0-10)	4 w	-1.2 (-2.0 to -0.3)	0.01
	6 w	-1.4 (-2.4 to -0.5)	0.004
	12 w	-1.2 (-2.2 to -0.2)	0.02
NRS pain (walking) (0-10)	4 w	-1.0 (-1.9 to -0.1)	0.03
	6 w	-1.2 (-2.2 to -0.3)	0.008
	12 w	-1.1 (-2.1 to-0.1)	0.03
WOMAC pain (0-100)	4 w	-5.5 (-12.6 to 1.6)	0.13
	6 w	-8.5 (-15.9 to -1.0)	0.03
	12 w	-8.2 (-16.4 to 0.0)	0.05
WOMAC function (0-100)	2 w	-6.5 (-14.1 to 1.1)	0.09
	4 w	-8.4 (-16.1 to -0.6)	0.03
	6 w	-7.3 (-15.4 to 0.6)	0.07
	12 w	-8.2 (-16.9 to 0.5)	0.06
WOMAC stiffness (0-100)	2 w	-7.1 (-15.3 to 1.0)	0.09
	4 w	-9.4 (-18.3 to -0.6)	0.04
	6 w	-8.7 (-18.0 to 0.6)	0.07
	12 w	-9.7 (-19.7 to 0.2)	0.06
WOMAC total (0-100)	2 w	-6.2 (-13.2 to 0.9)	0.08
	4 w	-7.6 (-14.9 to -0.3)	0.04
	6 w	-7.8 (-15.5 to -0.0)	0.05
	12 w	-8.3 (-16.8 to 0.1)	0.05
HOOS pain (0-100)	2 w	4.7 (-2.1 to 11.6)	0.18
	4 w	4.5 (-2.4 to 11.4)	0.20
	6 w	7.1 (-0.1 to 14.3)	0.05
	12 w	6.8 (-1.1 to 14.8)	0.09
HOOS ADL (0-100)	2 w	6.5 (-1.1 to 14.1)	0.09
	4 w	8.4 (0.6 to 16.1)	0.03
	6 w	7.4 (-0.6 to 15.4)	0.07
	12 w	8.2 (-0.5 to 16.9)	0.06
ICOAP intermittent (0-100)	2 w	-7.5 (-15.2 to 0.1)	0.05
	4 w	-9.5 (-17.4 to -1.6)	0.02
	6 w	-12.7 (-20.8 to -4.6)	0.002
	12 w	-11.4 (-20.0 to -2.9)	0.009

Appendix A Unadjusted results of the multivariable linear mixed model analysis with repeated measurements regarding primary and secondary outcomes between the corticosteroid and placebo group. (continued)

		Difference * (95% CI)	p- value
ICOAP constant (0100)	2 w	-8.5 (-16.4 to -0.5)	0.04
	4 w	-9.2 (-17.5 to -0.8)	0.03
	6 w	-10.8 (-19.2 to -2.4)	0.01
	12 w	-11.1 (-19.5 to -2.8)	0.009
ICOAP total (0-100)	2 w	-8.0 (-15.1 to -0.8)	0.03
	4 w	-9.4 (-17.1 to -1.6)	0.02
	6 w	-11.9 (-19.7 to -4.0)	0.003
	12 w	-11.3 (-19.4 to -3.3)	0.006
quality of life EQ-5D	2 w	0.061 (-0.007 to 0.129)	0.08
	4 w	0.037 (-0.004 to 0.123)	0.39
	6 w	0.071 (-0.002 to 0.144)	0.06
	12 w	0.088 (-0.002 to 0.178)	0.06

* placebo group is reference group; SD = standard deviation; 95%CI = 95% confidence interval; WOMAC = Western Ontario and McMaster Universities Index (0 = no pain); NRS = Numerical Rating Scale (0 = no pain); HOOS = Hip disability and Osteoarthritis Outcome Score (0 = extreme problems); ICOAP = intermittent and constant osteoarthritis pain (0= no pain); EQ-5D = Euroqol; w = weeks

Appendix B Co-interventions in the two study groups

Frequent pain medication use*		Corticosteroid (n= 52)	Placebo (n= 54)
Acetaminophen, n (%)	2 w	19 (37)	25 (46)
	4 w	21 (40)	26 (48)
	6 w	19 (37)	24 (45)
	12 w	19 (37)	25 (49)
NSAID, n (%)	2 w	13 (25)	11 (20)
	4 w	12 (23)	13 (24)
	6 w	9 (18)	12 (23)
	12 w	12 (24)	11 (22)
Opiates, n (%)	2 w	8 (15)	8 (15)
	4 w	7 (14)	8 (15)
	6 w	6 (12)	7 (13)
	12 w	5 (10)	6 (12)
Visited healthcare giver for hip OA, n (%)			
General practitioner Number of visits (median, range)	2 w	2 (4) 1 (1-1)	3 (6) 1 (1-2)
	4 w	1 (2) 1 (1-1)	5 (9) 1 (1-2)
	6 w	1 (2) 1 (1-1)	1 (2) 1 (1-1)
	12 w	3 (6) 1 (1-2)	0 --
Physiotherapist Number of visits (median, range)	2 w	9 (17) 2 (1-4)	7 (13) 1 (1-4)
	4 w	8 (15) 1.5 (1-2)	8 (15) 1 (1-4)
	6 w	10 (20) 1 (1-4)	8 (15) 1.5 (1-4)
	12 w	7 (14) 2 (1-4)	9 (18) 1 (1-3)
Medical specialist Number of visits (median, range)	2 w	2 (4) 1 (1)	2 (4) 1 (1)
	4 w	0 --	1 (2) 1 (1)
	6 w	2 (4) 1 (1)	3 (6) 1 (1)
	12 w	2 (4) 1.5 (1-2)	2 (4) 1 (1)

* Frequent pain medication use = 3-5 times/week or daily use in the past 2 weeks; NSAID = non-steroidal anti-inflammatory drug; w = weeks

CHAPTER 4

Is anesthetic hip joint injection useful in diagnosing hip osteoarthritis? A meta-analysis of case series.

DMJ Dorleijn, PAJ Luijsterburg, SMA Bierma-Zeinstra, PK Bos

Journal of Arthroplasty 2014, Jun 29(6) 1236-1242

Abstract

Background: To assess the diagnostic value of intra-articular anesthetic hip injection in patients with hip pain atypical for osteoarthritis (OA), literature was searched.

Methods: Included were studies assessing the diagnostic value of anesthetic hip injections in differentiating between pain caused by OA or another source. Pooled estimates of sensitivity and specificity with 95% confidence intervals (CI) were calculated.

Results: Of the 1387 potentially eligible articles, nine case series with high risk of bias could be included. The pooled sensitivity was 0.97 (95% CI 0.87 - 0.99). Specificity was 0.91 (95% CI 0.83 - 0.95).

Conclusions: For clinical practice, no recommendation can be made regarding the use of hip injections for diagnosing hip OA. High quality, accurately reported studies are needed to provide better evidence on the diagnostic role of hip injection.

Introduction

Pain in the hip region can arise from different sources, including intra-articular hip joint pathologies such as osteoarthritis (OA), synovitis, femoroacetabular impingement and labral pathology, as well as extra-articular causes such as greater trochanter pain syndrome, inguinal hernia, and referred pain or radicular pain from the lumbosacral spine and sacroiliac joints.

Although careful history taking and physical examination can often differentiate between hip OA and other sources, signs and symptoms are sometimes atypical, causing a diagnostic dilemma. Previous research provided evidence for an association between hip pain and disk space narrowing at disk level L1/L2 and L2/L3.[1] Moreover, the severity of radiographic hip OA does not always correlate with the symptoms.[2, 3]

Because therapy considered for end-stage hip OA includes total hip replacement (THR) surgery, it is essential to correctly evaluate the signs and symptoms.

Intra-articular anesthetic hip injection is an additional diagnostic tool to exclude or confirm an intra-articular source of hip pain.[4-8] Although this test is widely used in orthopaedic practice, the diagnostic value of this injection is not well established and most studies included small numbers of participants.

The objective of this meta-analysis is to assess the diagnostic value of intra-articular anesthetic hip injection when differentiating between hip pain caused by hip OA or an alternative source in patients with hip pain atypical for OA.

Methods

Search strategy

A search was performed (1966 until end December 2011) in PubMed, Embase, PEDro, and the Cochrane Library (Cochrane database of systematic reviews, database of abstracts of reviews of effects, and Cochrane central register of controlled trials) to identify studies evaluating the diagnostic value of an anesthetic hip joint injection when differentiating between hip pain caused by OA, or a spinal source or another source, in patients with atypical hip pain. The databases were searched using a combination of different terms for the following items: "OA", "hip", "spine", "diagnostic" and "intra-articular". A detailed description of the full electronic search strategies is provided in Appendix A.

Eligibility criteria

We included all cohort studies, including randomized controlled trials and case series about adults with hip pain that was possibly caused by degenerative hip disease, and who had been given an anesthetic diagnostic injection in the hip joint. The study had to report original data

on a function score or pain score after the diagnostic injection, as well as a function score or pain score after further therapy, e.g. THR, spinal treatment.

Study selection

To identify potentially relevant studies, two authors (DD and PKB) independently evaluated the title and abstract on the basis of the eligibility criteria. Full-text articles were screened for eligibility and the reference lists of these articles were searched for additional articles. Disagreement was solved by discussion.

Data extraction

One author (DD) extracted the data using a standardized form. Extracted data were checked by a second author (PL). The following data were collected: demographic and clinical characteristics (design, age and participant characteristics), how the anesthetic hip injection was given, the reference tests used, outcomes after consecutive therapy, and the duration of follow-up.

Assessment risk of bias

The included studies were assessed for their methodological quality by two authors (PL and SB), independently of each other, using the QUADAS2.[9] The QUADAS2 is a recently introduced improvement of the QUADAS[10] which was developed for quality assessment of diagnostic studies. The QUADAS2 consists of four domains covering the following items: patient selection, index test, reference standard, and flow and timing. Each item was scored for risk of bias (risk of bias indicated as low, high or unclear). If the answers to all signaling questions for a domain are "yes," then risk of bias was judged as low. In the domain 'patient selection' the risk of bias was also judged as low if the first question was answered with "unclear" and the second and third questions with "yes". If any signaling question was answered with "no," the risk of bias was judged as high. Any other combination of answers to the signaling questions for a domain was judged as unclear.

The items patient selection, index test, and reference standard were also scored for concerns regarding applicability (low, high or unclear concern).[9] Disagreement was solved by discussion (Appendix B).

Outcomes and meta-analyses

Pain relief after THR was used as the main outcome measurement. Pain relief after other therapy (e.g. spinal treatment) was used as a secondary outcome. Diagnostic two-by-two tables were extracted or reconstructed using relevant data of the included studies. For each study, results are presented as sensitivity, specificity, positive predictive value and negative predictive value of the index test (intra-articular anesthetic hip injection).

Depending on clinical homogeneity of the included studies, we calculated pooled estimates of sensitivity, specificity, positive likelihood ratio and negative likelihood ratio with the 95% confidence intervals (CI) of the diagnostic test (intra-articular anesthetic hip injection) for predicting pain relief after subsequent therapy including THR and for predicting pain relief after THR only.

Additionally, we performed a best-case and worst-case scenario analysis. In the best-case scenario, patients who reported pain relief after the diagnostic injection with no THR were considered true positive; and those who did not have pain relief after the diagnostic injection with unknown diagnosis were considered true negative. In the worst-case scenario, patients reporting pain relief after the diagnostic injection and no THR were considered false positive, and those with no pain relief after the diagnostic injection with unknown diagnosis were considered false negative. STATA version 12 was used to calculate pooled estimates.

Kappa statistics were used to calculate agreement between investigators for risk of bias of the selected studies (0–0.5 indicates a poor level of agreement, 0.5 to 0.7 indicates a moderate level of agreement, 0.7 and above indicates a high level of agreement).

Results

Study selection

The literature search yielded 1387 potentially eligible studies. Finally, 9 articles representing 556 patients with hip pain were included in the systematic review (Fig. 1).[4-8, 11-14]

Study characteristics

Table 1 presents the characteristics of the studies. Most studies included patients with concomitant hip and spine pathology or with inconclusive clinical and radiologic examinations, resulting in a diagnostic dilemma. The intra-articular hip injection was often used as a discriminative diagnostic to decide whether the patient should receive a THR. Two studies had a prospective design.[7, 11] Three different anesthetic agents were used: bupivacaine, lidocaine and marcaine; three studies combined the anesthetic agent with a corticosteroid. [5, 8, 13]

Pain relief after THR was scored with different measurement tools; only three studies used a validated scoring system for pain relief such as the Harris Hip Score (HHS) and a visual analogue scale (VAS).[6, 8, 14] None of the nine studies reported a validated measurement to evaluate pain relief following therapies for alternative diagnoses. Length of follow-up was not specified in three studies, and in the others ranged from 6 weeks to 65 months.

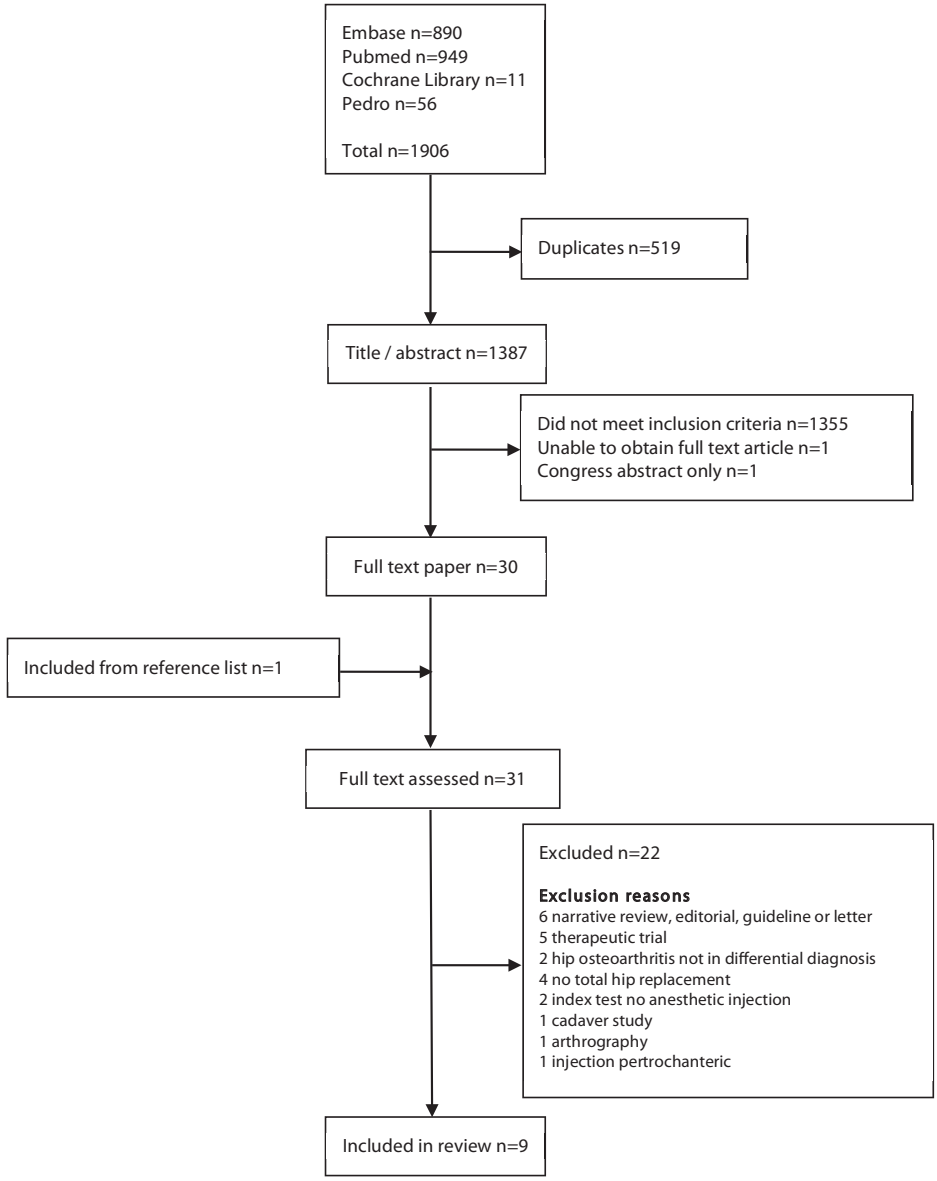


Figure 1 Flowchart of the selection of included studies.

Table 1 Characteristics of studies evaluating the diagnostic value of intra-articular hip injection in patients with atypical hip pain.

Study	n	Design	Purpose of study	Mean age in years (range)	Participant characteristics	Index test	control of IA injection	Reference test	FU	Outcome after injection	Outcomes after subsequent therapy	Adverse reactions
Ashok et al.[11]	48	Prospective Case series	to establish value of IA hip injection to clarify source of pain in patients with hip and spinal pathology	66 (41-83)	clinical and/or radiol^ hip and spinal pathology	bupivacaine 0.5% max. 10 ml	under fluoroscopic guidance	THR; spinal treatment	19 M	pain relief (+ = >70% relief; - = <30% relief)	satisfactory relief symptoms; no complications	no adverse reactions
Crawford et al.[4]	42	Case series	to establish whether IA hip injection was valuable to clarify source of pain in patients with minimal radiologic changes and in patients with concomitant spinal pathology	not reported	diagnosis of hip OA in doubt	marcaine 0.5% max. 10 ml	no control of intra-articular position	THR	6 W	pain	pain relief; satisfaction after THR	temporary palsy femoral nerve (n=1)
Faraj et al.[5]	47	Retrospective Case series	to evaluate diagnostic value of local anaesthetics with or without steroid in establishing the source of pain when the clinical and radiological features were inconclusive	57 (28-86)	pain around hip; borderline clinical or radiol features; coexistent spine involvement	bupivacaine & triamcinolon acetate	under fluoroscopic guidance	THR; other therapy	not reported	complete/ significant pain relief	pain relief	hip pain deteriorated after injection (n=2)
Illgen et al.[6]	30	Retrospective Case series	to assess the diagnostic and predictive value of hip anaesthetic arthrograms in patients with concurrent hip and spine pathology	67 (47-83)* 72 (50-85)**	hip/spine: atypical; radiol concurrent; failure conservative therapy	lidocaine 2% and bupivacaine 0.5%	under fluoroscopic guidance	THR; spinal treatment	min. 1Y	VAS pain (+ = min. 50% relief; - = <50% relief)	VAS/HHS; satisfaction	vasovagal reaction (n=1)
Kleiner et al.[7]	18	Prospective Case series	to describe experience with IA hip injection to differentiate in patients presenting with extremity pain below the knee and coexistent OA of lumbar spine and hip	68 (59-79)	pain extending below the knee; radiol concurrent hip and spine OA	bupivacaine 0.25% 10 ml	only injection under fluoroscopic guidance if 'blind' injection did not result in pain relief	THR; spinal treatment	not reported	pain relief (3-point scale)	not reported	no adverse reactions

Table 1 Characteristics of studies evaluating the diagnostic value of intra-articular hip injection in patients with atypical hip pain. (continued)

Study	n	Design	Purpose of study	Mean age in years (range)	Participant characteristics	Index test	control of IA injection	Reference test	FU	Outcome after injection	Outcomes after subsequent therapy	Adverse reactions
Odoom et al.[12]	60	Retrospective Case series	to compare the outcome of hip therapy with IA anaesthetic injection	58 (8-88)	patients who had undergone hip arthrogram	bupivacaine max. 5 ml	under fluoroscopic guidance	THR	not reported	pain relief (4-point scale)	pain relief after THR; no significant complications	injection subcutaneous (n=18); recurrent dislocation THR (n=1)
Pateder et al.[8]	83	Retrospective Case series	to differentiate the major pain generator in patients with concomitant hip and spine arthritis using IA bupivacaine and triamcinolone hip injection	63 (32-83)	concomitant hip and spine arthritis; atypical pain	lidocaine and triamcinolon acetate	under fluoroscopic guidance	THR; spinal treatment	min. 2Y	VAS; HHS (+ = VAS>3 or HHS significant improved)	substantial improvement VAS/HHS	not reported
Poiraudeau et al.[13]	90	Retrospective Case series	to differentiate the main origin of the pain in patients with hip and spine OA using IA hip injection	61 (33-89)	radiol evidence hip and spine OA	lidocaine 2% max. 10 ml; cortival 0.3 mg***	under fluoroscopic guidance	THR; effect cortival	6-65 M	min. 75% pain relief	outcome of treatment (5-point scale)	no adverse reactions
Yoong et al.[14]	138	Retrospective Case series	to establish whether the use of diagnostic ultrasound guided IA hip injection can localize pathology and guide treatment in patients with possible hip OA	68 (19-87)	diagnosis hip OA in doubt	bupivacaine 0.25% max. 10 ml	by ultrasound	THR; alternative diagnosis	1Y	pain relief (3-point scale)	modified HHS; outcome surgery (3-point scale); alternative diagnosis	transient femoral nerve block (n=1); septic arthritis (n=1)

* responders; ** non responders; ^ radiol = radiologic; *** cortival was sometimes used, but authors do not specify when; IA= intra-articular; THR = total hip replacement; min. = minimum; max. = maximum; FU=follow-up; M=months; W=weeks; Y=years; VAS = visual analogue scale; HHS = Harris Hip Score

Risk of bias

The quality assessment of the individual studies is presented in Table 2. Inter-observer agreement for signaling questions was high (κ 0.72). Inter-observer agreement for each domain was moderate (κ 0.69). The reporting on whether the reference standard results were interpreted without knowledge of the results of the index test was poor in all studies. Because not all patients received the reference standard (THR), in all studies there was a high risk of verification bias.

Table 2 Risk of bias assessment.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ashok et al. [11]	L	L	U	H	L	H	U
Crawford et al. [4]	U	U	U	H	U	L	H
Faraj et al. [5]	U	H	U	H	L	U	H
Illgen et al. [6]	L	L	U	H	L	H	L
Kleiner et al. [7]	U	U	U	H	H	L	H
Odoom et al. [12]	U	U	U	H	H	H	H
Pateder et al. [8]	L	H	U	H	H	U	L
Poiraudeau et al. [13]	U	L	U	H	L	H	H
Yoong et al. [14]	L	U	U	H	L	H	L

L = low; H = high; U = unclear

Outcome of the diagnostic test

Yoong et al used three different categories to rank the relief of pain after the diagnostic injection (complete relief, partial relief and no relief of pain); they also used these three categories to determine pain relief after subsequent therapy.[14] Odoom et al did not report the strategy for patients who did not have relief of pain after the diagnostic injection.[12] Neither of these two studies reported the sensitivity and specificity of the intra-articular anesthetic injection.[12, 14]

In the other studies,[4-8, 11, 13] the sensitivity of the intra-articular anesthetic hip injection to predict pain relief after THR ranged from 0.78 (95% CI 0.56 - 0.93) to 1.00 (95% CI 0.95 - 1.00) and specificity to predict pain relief after THR ranged from 0.67 (95% CI 0.22 - 0.96) to 1.00 (95% CI 0.03 - 1.00) (Table 3). The positive predictive value ranged from 0.90 to 1.00 and the negative predictive value from 0.33 to 1.00.

Table 3 Sensitivity, specificity and predictive values of the included studies for the intra-articular anesthetic hip injection to predict pain relief after THR.

Study	Sensitivity (95% CI)*	Specificity (95% CI)	Positive predictive value	Negative predictive value
Ashok et al. [11]	0.97 (0.85 - 1.00)	0.91 (0.59 - 1.00)	0.97	0.91
Crawford et al. [4]	1.00 (0.89 - 1.00)	1.00 (0.66, 1.00)	1.00	1.00
Faraj et al. [5]	0.89 (0.71 - 0.98)	1.00 (0.80 - 1.00)	1.00	0.85
Illgen et al. [6]	0.95 (0.76 - 1.00)	0.88 (0.47 - 1.00)	0.95	0.88
Kleiner et al. [7]	0.88 (0.64 - 0.99)	1.00 (0.03 - 1.00)	1.00	0.33
Odoom et al. [12]	NE	NE	0.94	NE
Pateder et al. [3]	1.00 (0.95 - 1.00)	0.82 (0.48 - 0.98)	0.97	1.00
Poiraudeau et al. [13]	0.78 (0.56 - 0.93)	0.67 (0.22 - 0.96)	0.90	0.44
Yoong et al. [14]	NE	NE	NE	NE

* CI = confidence interval; NE = not estimable

Meta-analysis

The data of seven studies were pooled to calculate pooled estimates of sensitivity, specificity and likelihood ratios. Two studies were not included in the meta-analysis.[7, 12] The study of Odoom et al was excluded because it did not report the outcome pain relief of patients who responded negatively to diagnostic injection.[12] In the study of Kleiner et al, no patients with a false-positive response were reported;[7] also, as we could not calculate the specificity for this latter study, it was excluded from the meta-analysis.

Rather than reporting sensitivity and specificity, Yoong et al used three outcome categories after intra-articular injection and after surgery.[14] In order to use their data in the meta-analysis, we dichotomized both outcomes by combining complete and partial within a single category. In the study of Crawford et al one patient died 10 days after THR;[4] thus, because the outcome after surgery is unknown this patient was also excluded from the meta-analysis.

Although 476 patients were available for the meta-analysis, data on pain relief after final therapy were missing for 125 patients: 75 patients who responded positively to the injection did not get a THR, and the diagnosis and treatment of 50 patients who responded negatively to the injection were unknown.

Therefore, a meta-analysis was performed with 351 patients with a pain outcome after THR, or after therapy for other diagnoses (Table 4).

A positive response to the diagnostic hip injection had pooled estimates of 0.97 (95% CI 0.87 - 0.99) for sensitivity and of 0.91(95% CI 0.83 - 0.95) for specificity for predicting pain relief after subsequent therapy including THR. This corresponds to a positive likelihood ratio (LR+) of 10.6 (95% CI 5.6 - 20.1) and a negative likelihood ratio (LR–) of 0.04 (95% CI 0.01 - 0.15). Fig. 2A shows the Receiver Operating Curve (ROC) of this meta-analysis.

Table 4 Meta-analysis of the included studies.

Pool	Studies included	n	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Pooled positive likelihood ratio (95% CI)	Pooled negative likelihood ratio (95% CI)
All outcomes	7	351	0.97 (0.87 - 0.99)	0.91 (0.83 - 0.95)	10.6 (5.6 - 20.1)	0.04 (0.01 - 0.15)
Best case	7	476	0.97 (0.91 - 0.99)	0.93 (0.87 - 0.97)	14.7 (7.3 - 29.8)	0.03 (0.01 - 0.10)
Worst case	7	476	0.89 (0.70 - 0.97)	0.68 (0.33 - 0.90)	2.8 (1.0 - 7.5)	0.16 (0.04 - 0.57)
THR only	7	269	0.96 (0.87 - 0.99)	0.42 (0.09 - 0.84)	1.7 (0.7 - 3.8)	0.09 (0.02 - 0.41)

4 different analyses were conducted: All outcomes: this includes pain score after total hip replacement (THR) and pain score after other therapy; Best case: patients who responded positively to the injection that did not get a THR were categorized as true positive, and patients who responded negatively to the injection with unknown diagnosis were categorized as true negative; Worst case: patients who responded positively to the injection that did not get a THR were categorized as false positive, and patients who responded negatively to the injection with unknown diagnosis were categorized as false negative; THR only: patients who received a THR were analyzed

Additional analyses were performed for three different scenarios: a best-case scenario, a worst-case scenario and a THR-only scenario.

The best-case scenario included patients who responded positively to the injection that did not get a THR as true positive, and those who responded negatively to the injection with unknown diagnosis as true negative. The pooled estimates of sensitivity and specificity were 0.97 (95% CI 0.91 - 0.99) and 0.93 (95% CI 0.87 - 0.97) for predicting pain relief after subsequent therapy including THR. This corresponds to an LR + of 14.7 (95% CI 7.3 - 29.8) and an LR– of 0.03 (95% CI 0.01 - 0.10).

The worst-case scenario included patients who responded positively to the injection that did not get a THR as false positive, and those who responded negatively to the injection with unknown diagnosis as false negative. The pooled estimates of sensitivity and specificity were 0.89 (95% CI 0.70 - 0.97) and 0.68 (95% CI 0.33 - 0.90) for predicting pain relief after subsequent therapy including THR. This corresponds to an LR + of 2.8 (95% CI 1.0 - 7.5) and an LR– of 0.16 (95% CI 0.04 - 0.57).

The THR-only scenario included patients who had received a THR and whose pain outcome was scored afterwards. These results are plotted in Fig. 2B. The pooled estimates of sensitivity and specificity for the intra-articular anesthetic injection were 0.96 (95% CI 0.87 - 0.99), and 0.42 (95% CI 0.09 - 0.84) for predicting pain relief after THR. This corresponds to an LR + of 1.7 (95% CI 0.7 - 3.8) and an LR– of 0.09 (95% CI 0.02 - 0.41).

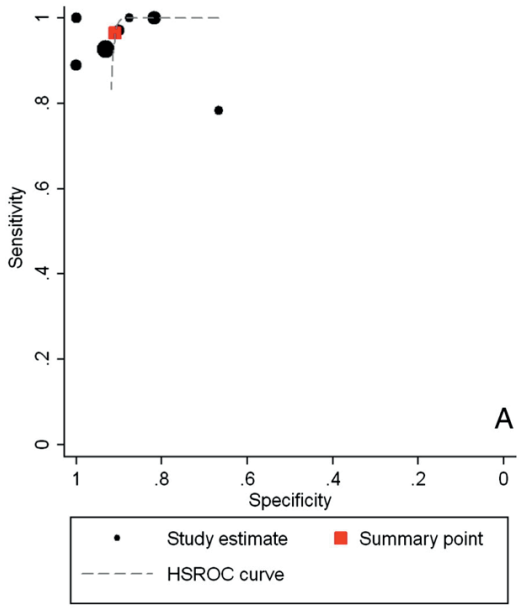


Fig 2A Receiver Operating Curve (ROC) of pooled data; pain outcomes after total hip replacement and after other therapy.
HSROC = hierarchical summary receiver operating characteristic

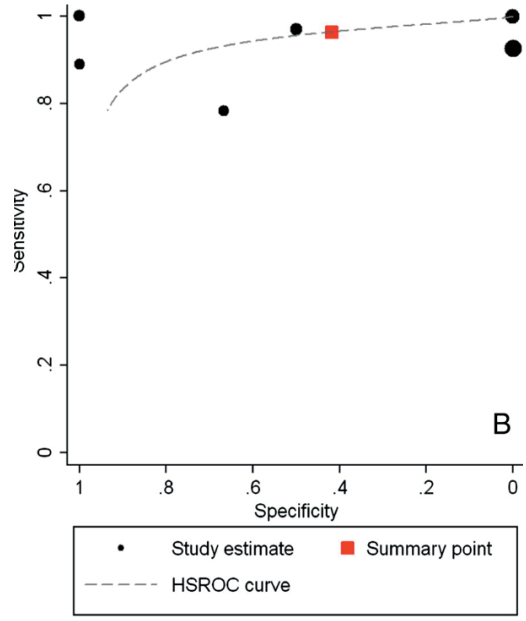


Fig 2B Receiver Operating Curve (ROC) of pooled data; pain outcomes after total hip replacement.
HSROC = hierarchical summary receiver operating characteristic

Discussion

This meta-analysis summarizes the available evidence on the diagnostic value of intra-articular anesthetic hip injection in differentiating between hip pain caused by OA, spinal sources or other sources in adult patients with atypical hip pain.

Of the 1387 potentially eligible articles only 9 studies, with low-to-medium quality, met the inclusion criteria. The pooled results (of 7 studies) show that if the injection has a negative effect on pain relief, then this is predictive for no pain relief after THR (sensitivity of 0.97 (95% CI 0.87 - 0.99)). On the other hand the specificity ranged from 0.42 (95% CI 0.09 - 0.84) to 0.91 (95% CI 0.83 - 0.95) and indicates that it is uncertain to predict pain relief after THR.

Strengths and weaknesses

An important problem of the included studies is the reference standard. All studies use THR as reference standard, but also had partial verification bias. For example, in our pooled analyses, patients who responded positively to the diagnostic injection received a THR in 75% of the cases, whereas for patients who responded negatively to the injection only 15% received a THR. Similarly seven of the nine studies use pain outcomes after other therapy as a second gold standard; however, because these 'other' therapies are not well described, the outcomes are difficult to interpret. Also, low-back pain therapies might be less effective, even when the diagnosis is correct.[15, 16] Verification bias might lead to higher sensitivity and lower specificity, but our analyses show that both sensitivity and specificity increased.[17]

An important source of heterogeneity was the index test used (anesthetic injection). In three studies the anesthetic agent was combined with a corticosteroid.[5, 8, 13] Intra-articular corticosteroids have a beneficial effect on pain in hip OA and this effect is already present one week after injection.[18] Since two of three studies review the effect of the diagnostic injection on pain at two weeks follow-up, this might have increased the number of patients reporting pain relief.[5, 8] In sensitivity analysis, we excluded studies that combined the anesthetic agent with corticosteroids; this resulted in four included studies with a total of 219 patients.[4, 6, 11, 14] The pooled estimates of sensitivity and specificity were 0.97 (95% CI 0.87 - 0.99), and 0.92 (95% CI 0.81 - 0.97), respectively, which are similar to our results (Table 4).

Another source of heterogeneity was the measurement of the outcome pain. Patients' perceived pain after THR was measured at different time points during follow-up (ranging from 6 weeks to 65 months) and with various measuring instruments, such as a 5-point scale, patients' satisfaction, and occurrence of complication. Only three studies used a validated instrument to measure pain (HHS, VAS).[6, 8, 14] We would recommend a follow-up after THR of at least 6 months.

Finally, a large percentage of data was missing in the meta-analysis. Perceived severity of hip pain after injection and after subsequent therapy was unclear for 125 (26%) of 476

patients. A positive response to the injection was reported for 75 of these 125 patients, but they did not receive a THR; although the authors provided two explanations for this, none of the studies recorded the reasons in a structured way. The explanations given were: patients' refusal of surgery, and patients being too young to receive a THR. Of the 125 patients, 50 (40%) responded negatively to the injection, but the final diagnosis and treatment were not described. Our analysis of the best-case scenario and worst-case scenario revealed the influence of these missing data.

There was a high inter-observer agreement in quality assessment of the included articles. Because the QUADAS2 was recently published, it has not been extensively used and comparison with other reviews using this second version is not yet possible. However, the interobserver agreement presented by Whiting et al in their QUADAS2 article showed a considerable range (overall kappa for the four domains 0.00 to 1.00);[9] they did not assess the agreement for signaling questions.

Implications for clinical practice and research

An intra-articular anesthetic hip injection is a diagnostic test that is used in a patient group with atypical signs and symptoms when diagnosis of hip OA is difficult to establish. It is used in orthopaedic practice with significant implications for treatment strategy: including the decision for a THR.

This review indicates that there is little evidence available for the use of intra-articular injections for the diagnosis of hip OA (9 out of 1387 studies). Moreover, the available evidence had a high risk of bias. Based on the available evidence, we can only very cautiously conclude that a negative effect on pain relief is predictive for no pain relief after THR. On the other hand with a positive effect on pain relief after injection it is uncertain to predict pain relief after THR. For clinical practice, no recommendation can be made regarding substantiated favoring or not favoring the use of intra-articular injections for the diagnosis of hip OA.

High quality and accurately reported diagnostic studies are needed to provide better evidence on the role of intra-articular anesthetic hip injection in differentiating between hip OA, spinal source and other sources of pain. Therefore, future studies, preferably a well-designed large prospective cohort, should place more focus on the subsequent treatment and outcome(s) of patients who responded negatively to the diagnostic injection.

References

1. de Schepper EI, Damen J, Bos PK, Hofman A, Koes BW, Bierma-Zeinstra SM. Disk degeneration of the upper lumbar disks is associated with hip pain. Eur Spine J 2013; 22: 721-726.
2. 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. Rheum 2005; 44: 337-341.
3. Reijman M, Hazes JM, Pols HA, Bernsen RM, Koes BW, Bierma-Zeinstra SM. Validity and reliability of three definitions of hip osteoarthritis: cross sectional and longitudinal approach. Ann Rheum Dis 2004; 63: 1427-1433.
4. Crawford RW, Gie GA, Ling RS, Murray DW. Diagnostic value of intra-articular anaesthetic in primary osteoarthritis of the hip. J Bone Joint Surg Br 1998; 80: 279-281.
5. Faraj AA, Kumaraguru P, Kosygan K. Intra-articular bupivacaine hip injection in differentiation of coxarthrosis from referred thigh pain: a 10 year study. Acta Orthop Belg 2003; 69: 518-521.
6. Illgen RL, 2nd, Honkamp NJ, Weisman MH, Hagenauer ME, Heiner JP, Anderson PA. The diagnostic and predictive value of hip anesthetic arthrograms in selected patients before total hip arthroplasty. J Arthroplasty 2006; 21: 724-730.
7. Kleiner JB, Thorne RP, Curd JG. The value of bupivicaine hip injection in the differentiation of coxarthrosis from lower extremity neuropathy. J Rheumatol 1991; 18: 422-427.
8. Pateder DB, Hungerford MW. Use of fluoroscopically guided intra-articular hip injection in differentiating the pain source in concomitant hip and lumbar spine arthritis. Am J Orthop 2007; 36: 591-593.
9. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155: 529-536.
10. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003; 3: 25.
11. Ashok N, Sivan M, Tafazal S. The diagnostic value of anaesthetic hip injection in differentiating between hip and spinal pain. Eur J Orhop Surg Traumatol 2009: 167-171.
12. Odoom JE, Allen GM, Wilson DJ. Response to local anaesthetic injection as a predictor of successful hip surgery. Clin Radiol 1999; 54: 430-433.
13. Poiraudeau S, Martinez M, Anract P, Chevrot A, Revel M. Value of hip anesthesia to characterize the main origin of pain in hip-spine osteoarthritis. Europa Medicophysica 2000; 36: 61-66.
14. Yoong P, Guirguis R, Darrah R, Wijeratna M, Porteous MJ. Evaluation of ultrasound-guided diagnostic local anaesthetic hip joint injection for osteoarthritis. Skeletal Radiol 2012; 41: 981-985.
15. Luijsterburg PA, Verhagen AP, Ostelo RW, van Os TA, Peul WC, Koes BW. Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review. Eur Spine J 2007; 16: 881-899.
16. van Middelkoop M, Rubinstein SM, Kuijpers T, Verhagen AP, Ostelo R, Koes BW, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. Eur Spine J 2011; 20: 19-39.
17. Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med 2004; 140: 189-202.
18. Atchia I, Kane D, Reed MR, Isaacs JD, Birrell F. Efficacy of a single ultrasound-guided injection for the treatment of hip osteoarthritis. Ann Rheum Dis 2011; 70: 110-116.

Appendix A Description of the electronic search strategies.

PubMed	(((osteoarthritis[tw] OR bursitis[tw] OR degenerative joint disease[tw]) AND (hip[tiab] OR hip[mh] OR hip joint[mh] OR spine[tw] OR lumbar vertebrae[tw])) OR Back pain*[tw] OR hip pain*[tw] OR backache*[tw] OR back-ache*[tw] OR Vertebrogenic Pain*[tw]) AND (Injections, Intra-Articular[tw] OR (injection*[tw] AND (anaesthetic[tw] OR anesthetic[tw] OR diagnostic[tw] OR back pain/diagnosis[mh] OR osteoarthritis/diagnosis[mh] OR bursitis/diagnosis[mh] OR intra-articular[tw] OR intraarticular[tw]))) NOT (editorial[pt] OR letter[pt]) NOT (animals[mh] NOT humans[mh])
Embase	osteoarthritis:de,ab,ti OR bursitis:de,ab,ti OR 'degenerative joint disease':de,ab,ti AND (hip:de,ab,ti OR 'hip joint':de,ab,ti OR spine:de,ab,ti OR 'lumbar vertebrae':de,ab,ti) OR (back NEXT/1 pain*):de,ab,ti OR (hip NEXT/1 pain*):de,ab,ti OR backache*:de,ab,ti OR (back NEXT/1 ache*):de,ab,ti OR (vertebrogenic NEXT/1 pain*):de,ab,ti AND ('intraarticular drug administration'/de OR ((injection* NEAR/5 (anaesthetic OR anesthetic OR diagnostic OR 'intra articular' OR intraarticular)):de,ab,ti OR 'backache'/exp/dm_di OR 'osteoarthritis'/exp/dm_di OR 'bursitis'/exp/dm_di AND injection*:de,ab,ti)) NOT (editorial:pt OR letter:pt) NOT ([animals]/lim NOT [humans]/lim)
Cochrane	("diagnos* in Title, Abstract or Keywords and hip in Title, Abstract or Keywords in Cochrane Database of Systematic Reviews")
PEDro	(diagnos* AND hip in Title, abstract)

Appendix B Risk of bias assessment.

QUADAS2: Domains and signaling questions		
Risk of bias		
Domain		
Patient selection		Q: Could the selection of patients have introduced bias?
	1	SQ: Was a consecutive or random sample of patients enrolled?
	2	SQ: Was a case-control design avoided?
	3	SQ: Did the study avoid inappropriate exclusions?
Index test		Q: Could the conduct or interpretation of the index test have introduced bias?
	1	SQ: Were the index test results without knowledge of the results of the reference standard?
	2	SQ: If a threshold was used, was it pre-specified?
Reference standard		Q: Could the reference standard, its conduct, or its interpretation have introduced bias?
	1	SQ: Is the reference standard likely to correctly classify the target condition?
	2	SQ: Were the reference standard results interpreted without knowledge of the results of the index test?
Flow and timing		Q: Could the patient flow have introduced bias?
	1	SQ: Was there an appropriate interval between the index test and the reference standard?*
	2	SQ: Did all patients receive a reference standard?
	3	SQ: Did patients receive the same reference standard?
	4	SQ: Were all patients included in the analysis?
Applicability		
Domain		
Patient selection		Q: Are there concerns that the included patients and setting do not match the review question?
Index test		Q: Are there concerns that the index test, its conduct, or its interpretation differs from the review question?
Reference standard		Q: Are there concerns that the target condition as defined by the reference standard does not match the question?

Q = question, SQ = signalling question

CHAPTER 5

Association between biochemical cartilage markers and clinical symptoms in patients with hip osteoarthritis: cohort study with two-year follow-up

DMJ Dorleijn, PAJ Luijsterburg, AC Bay-Jensen, AS Siebuhr, MA Karsdal, RM Rozendaal, PK Bos, SMA Bierma-Zeinstra

Osteoarthritis and Cartilage 2015, (23) 57-62

Summary

Objectives: To assess associations between uCTX-II or uCIIM and severity of hip pain in patients with mild-moderate hip osteoarthritis (OA) over a 2-year period, and establish whether the level of these biomarkers at baseline could estimate a specific trajectory of hip pain.

Design: A cohort study with a 2-year follow-up and 6-monthly measurements of urinary biomarkers (uCTX-II and uCIIM) and symptom severity. Patients were recruited from general practices. The primary outcome was hip pain, measured with the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) subscale and the Visual Analogue Scale (VAS). Associations between hip pain and biomarkers were assessed using linear mixed-model analysis for repeated measurements. Five previously identified pain trajectories were used as outcome to investigate whether the level of biomarkers at baseline could estimate membership in one of the trajectories using multinomial regression analysis.

Results: LoguCTX-II and loguCIIM were not associated with WOMAC pain or VAS pain during the 2-year follow-up. Patients in the highly progressive pain trajectory and the moderate pain trajectory were more likely to have a higher loguCTX-II at baseline (OR 6.7; 95% CI 1.6-28.2 and OR 4.8; 95% CI 1.0-22.8, respectively) than patients in the mild pain trajectory.

Conclusion: This study shows that in patients with mild-moderate hip OA the urinary biochemical markers uCTX-II and uCIIM are not cross-sectionally associated with hip pain during the 2-year follow-up. Because the uCTX-II level estimated a progressive or moderate hip pain trajectory, this correlation needs to be confirmed in additional patients with hip OA.

Introduction

Osteoarthritis (OA) is characterized by slowly progressive damage of synovial joint tissues, including cartilage destruction and alterations of the bone and synovial tissue. Signs and symptoms of OA include joint pain, stiffness and disability. Although radiography is used to confirm OA in clinical practice, specific OA signs (such as joint space narrowing) are only visible after significant cartilage degradation has taken place.[1]

Biochemical markers, or biomarkers, are defined as characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[2] The availability of biomarkers that can assist in diagnosing early-stage OA, predicting OA progression, and assessing therapeutic responses could improve early diagnosis and help monitor the effect of OA treatment. In OA, biomarkers of interest originate from bone, synovial tissue, and the articular cartilage.[3]

The articular cartilage is composed of two primary matrix proteins: type II collagen and aggrecan. During cartilage erosion, type II collagen is sequentially degraded by enzymes, as matrix metalloproteinases (MMP). The resulting protein fragments, called neoepitopes, are released into the circulation and excreted in the urine; these fragments could serve as biomarkers. Two of these biomarkers of type II collagen metabolism are type II collagen C-telopeptide (CTX-II) and MMP-derived CIIM. Urinary (u) CTX-II has been investigated most extensively and associations have been shown between uCTX-II and radiographic hip joint space narrowing, and between uCTX-II and hip pain.[4, 5] CIIM has recently been identified as a collagen type II neoepitope; serum CIIM levels are reported to be higher in individuals with knee OA than in those without knee OA.[6] Although CIIM was originally identified in urine by mass spectrometry, to date no study has clinically validated the marker in urine as a marker of OA.

Most previous studies have investigated the relationship between biomarkers and symptoms cross-sectionally,[5] or studied the relation between biomarkers and prediction of structural damage.[7] Moreover, because the performance of biochemical markers has been investigated more frequently in knee OA than in hip OA, our knowledge on the performance of biomarkers in hip OA is limited.[5]

Studying symptomatic progression requires repeated measurements and the ability to discriminate progressing disease from non-progressing disease. Latent class growth analysis (LCGA) has this ability and is a technique that finds clinically meaningful groups of people who are similar in their responses to measured variables, e.g., pain scores.[8] Recently, LCGA applied to a longitudinal dataset of patients with hip OA discriminated between five different pain trajectories over a 2-year period of follow-up, i.e., high pain, moderate pain, mild pain, regularly progressive pain and highly progressive pain.[8] If biomarkers could help in predicting which group patients belong to, this could be of considerable clinical value.

The objective of this study was to assess whether there is an association between uCTX-II or uCIIM and perceived hip pain of patients with mild-moderate hip OA, over a 2-year period with 6-monthly measurements of urinary biomarkers and hip pain. The secondary objective was to assess whether these biomarkers could help to estimate a specific trajectory of hip pain over the 2-year period.

Methods

Study population

The study population consisted of primary care patients diagnosed with hip OA (n= 222) who participated in a prospective randomized controlled trial that assessed the effect of glucosamine sulfate (the GOAL trial; ISRCTN54513166).[9-11] This trial recruited prevalent cases of patients with hip complaints from databases of general practices in the Netherlands. Patients were eligible if they met one of the American College of Rheumatology (ACR) criteria for hip OA.[12] Patients who had undergone or were awaiting total hip replacement (THR) surgery and patients with a Kellgren and Lawrence (KL) score of 4 were excluded.[13] Patients were also excluded if they had renal disease, liver disease, diabetes mellitus, or were already taking glucosamine. Also excluded were patients with a disabling comorbid disease that would make visits to the research center impossible, and those unable to complete questionnaires in Dutch.

Eligible patients were randomly assigned to receive either 1500 mg of oral glucosamine sulfate once daily or placebo over a period of 2 years. The Medical Ethics Committee of the Erasmus University Medical Center approved the study design, and all patients provided written informed consent. A detailed description of the study design and outcomes has been published elsewhere.[9-11] The GOAL trial showed that glucosamine sulfate was not superior to placebo in reducing symptoms and progression of hip OA. One of the secondary outcomes of this trial was biomarker level of CTX-II and a promising new marker CIIM assessed in urine samples.[10]

Biochemical markers

The biomarkers uCTX-II and uCIIM were measured in second morning void urine at five time points: at baseline, and at 6, 12, 18 and 24-months follow-up. The samples were stored at -80^{o}C. The samples were collected from September 2003 until March 2006. The samples were analyzed in 2010. Prior to measurement the urine samples were thawed, vortexed and spun down to first mix the samples and pellet potential debris. Prolonged storage test of the assays for up to 12 years showed no effect of storage on the levels of the biomarkers. Urinary CTX-II was measured by the commercially available Cartilaps® ELISA (IDS Nordic, Herlev, Denmark). Urinary CIIM was measured by an in-house constructed EIA targeting the neo-epitope

RDGAAGY derived from MMP cleavage of type II collagen.[6, 14] For both assays, intra- and interassay variations were <8 and <12% for the urine measurement. Samples were run in duplicates and repeated if CV% was >15%. Both markers were normalized for the amount of creatinine (creat) in the urine. If the level of creat was below the lower limit of detection, then the level was set to the lowest detectable level (1 umol/mL creat). In our trial we did not measure CTX-II and CIIM in serum.

Clinical outcomes

The outcome was severity of hip pain reported by the patient. This was measured 3-monthly during the 2-year follow-up with two validated measuring instruments: the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) subscale for hip pain and the Visual Analogue Scale (VAS; range 0-100, 0 indicates no pain, 100 indicates unbearable pain.[15] The WOMAC subscale was converted to a 0-100 score (0 indicates no symptoms, 100 indicates unbearable pain). The WOMAC is recommended by the Osteoarthritis Research Society International for use in clinical trials in patients with hip OA to measure pain severity. The WOMAC asks patients about their pain in the previous 2 days; the VAS pain was scored as the average hip pain during the previous 7 days. If patients had a THR during follow-up, available data were included in the analysis until surgery; data collected after surgery were assumed to be missing.

Pain trajectories

Recently, using the 3-monthly repeated pain measurements during 2-year follow-up, five distinct trajectories of hip pain were identified in the GOAL data.[8] The LCGA differentiated the following trajectories: mild pain (n=69), moderate pain (n= 31), high pain (n=31), regularly progressive pain (n= 48), and highly progressive pain (n= 42).

A more detailed description of the determination of these pain trajectories has already been published.[8] Three of these five trajectories started with low baseline pain scores; however, over time the trajectories show important differences. The 'mild pain' trajectory stayed at the same low pain level during the 2-year follow-up, the 'moderate' trajectory showed a moderate progression in pain score, and the 'highly progressive' trajectory showed a rapid progression in pain score.

Here, we used the pain trajectories as outcome to investigate whether the level of biomarkers at baseline could estimate membership in one of the trajectories.

Statistical analysis

Data were analyzed using multivariable linear mixed models for repeated measurement to assess the cross-sectional associations between patients' perceived hip pain and uCTX-II and/or uCIIM over the 2-year period. The linear mixed model adjusts for the within-patient cor-

relation for the outcomes at different measurements in each patient and uses each outcome from each patient as a separate observation.

To obtain a normal distribution of uCTXII pg/umol creat and uCIIM pg/umol creat, the natural logarithm of both was taken. The unstructured covariance structure was used, since this yielded the lowest Akaike's Information Criterium (AIC).

Covariates used in the model were: age, gender and body mass index (BMI). To minimise the bias in our estimation of the association between biomarker and pain we performed the 6-step approach by Pearl.[16] This yielded the following covariables: allocated treatment, duration of hip complaints (dichotomised to <3 years vs ≥3 years), presence of hand OA or knee OA and severity of radiologic hip OA. Knee OA and hand OA at baseline were defined as KL score ≥2 as seen on the X-ray. Radiologic hip OA was defined as OA of the index hip (KL ≥ 2) vs no radiologic hip OA (KL < 2). All covariates were included in the model as fixed factors.

A subgroup analysis was performed with patients with minimal radiologic hip OA (KL < 2) and patients with definite radiologic hip OA (KL ≥2).

Multinomial regression analysis was used to assess if the baseline level of biomarkers estimates the probability of membership in one of the five trajectories of hip pain. Due to the division into five pain trajectories, the study population per trajectory was relatively small (n= 31 to n= 69). Therefore, in the multinomial analysis we did not adjust for other baseline variables. However, we studied other baseline variables also using univariate multinomial regression analysis. Since we were interested in the additional value of an imaging marker (radiography), we performed an explorative analysis for uCTX-II and uCIIM adjusted for baseline radiographic hip OA. All analyses were conducted using SPSS version 20.0.

Results

Study population

The baseline characteristics of the 222 patients participating in the GOAL trial are presented in Table 1. The mean age was 63.4 (SD 9.0) years and 69.4% of patients were female. The mean WOMAC pain score was 34.2 (SD 23.1) and the mean VAS pain score was 32.4 (SD 25.9). The duration of hip complaints was ≥3 years in 119 (53.6%) patients; 108 (48.6%) patients had a minimum KL score of 2. Of all patients, 20 received a THR during follow-up.

Biochemical markers

The median uCIIM pg/umol creat was 61.7 (IQR 51.5) and the median uCTX-II pg/umol creat was 332 (IQR 355). At baseline, biomarkers for 197 (89%) patients were available for analysis, compared with 177 (80%) patients at 6-months follow-up, 190 (86%) at 12 months, 186 (84%) at 18 months and 187 (84%) patients at 24-months follow-up.

Table 1 Patient characteristics at baseline.

Characteristic		Patients (n=222)
Gender (n, %)	Female	154 (69.4)
Age in years (mean, SD)		63.4 (9.0)
Body mass index (kg/m^2) (mean, SD)		28.0 (4.7)
Duration of complaints (n, %)	<3 years	103 (46.4)
	≥3 years	119 (53.6)
Knee OA (KL ≥ 2) (n, %)		68 (30.6)
Hand OA (KL ≥ 2) (n, %)		116 (52.3)
Radiologic hip OA (n, %)	KL<2	114 (51.4)
	KL ≥ 2	108 (48.6)
uCIIM pg/umol creat (median, IQR)		61.7 (51.5)
uCTX-II pg/umol creat (median, IQR)		332 (355)
WOMAC pain (0-100)		34.2 (23.1)
WOMAC function (0-100)		35.1 (22.9)
WOMAC stiffness (0-100)		42.6 (25.2)
VAS hip pain (0-100)		32.4 (25.9)

KL = Kellgren & Lawrence grading of radiologic OA, uCIIM = type II collagen marker, uCTX-II = C-terminal telopeptides of type II collagen, creat = creatinine, WOMAC = Western Ontario and McMaster Universities (0 indicates no pain), VAS = Visual Analog Scale (0 indicates no pain), SD = standard deviation, IQR = inter-quartile range

Associations between clinical outcomes and biochemical markers

The results of the multivariable adjusted mixed-model analysis are presented in Table 2a. Neither loguCTX-II nor loguCIIM were cross-sectionally associated with WOMAC pain or VAS pain during the 2-year follow-up. Covariates associated with WOMAC pain were: BMI (coefficient 1.0; 95% CI 0.4-1.5), female gender (coefficient 8.1; 95% CI 2.4-13.8) and duration of complaints (coefficient 7.2; 95% CI 2.1-12.4). Covariates associated with VAS pain were: BMI (coefficient 1.1; 95% CI 0.5-1.7), female gender (coefficient 7.5; 95% CI 1.2-13.8), duration of complaints (coefficient 7.0; 95% CI 1.4-12.6) and radiologic hip OA (KL≥2) (coefficient 6.6; 95% CI 0.7-12.5).

The subgroup analysis of patients with definite radiographic OA (KL≥2) at baseline (n =108) showed a significant association between loguCTX-II and VAS pain (coefficient 17.1; 95% CI 7.7-26.5). The association between loguCTX-II and WOMAC pain was not significant in the definite radiographic OA group, nor were the associations between loguCIIM and WOMAC pain or VAS pain.

In the group with minimal radiographic OA at baseline (n= 114), no associations were found between loguCTX-II, loguCIIM and the pain scores (see Table 2b and c).

Table 2a Results of multivariate linear mixed model analysis of biochemical markers and symptom severity during 2 years of follow-up with 6-monthly measurements.

Variable	WOMAC pain (0-100) (n=213)		VAS pain (0-100) (n=213)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Gender (female)	**8.1 (2.4 - 13.8)**	**<0.01**	**7.5 (1.2 to 13.8)**	**0.02**
Age (years)	0.0 (-0.3 to 0.3)	0.90	0.1 (-0.3 to 0.4)	0.68
Body mass index (kg/m^2)	**1.0 (0.4 - 1.5)**	**<0.01**	**1.1 (0.5 - 1.7)**	**<0.01**
Duration of complaints (>3 years)	**7.2 (2.1 - 12.4)**	**<0.01**	**7.0 (1.4 - 12.6)**	**0.02**
Concomitant knee OA	1.4 (-4.5 to 7.3)	0.64	-2.9 (-9.3 to 3.5)	0.37
Concomitant hand OA	-3.4 (-9.1 to 2.3)	0.24	-2.7 (-8.9 to 3.5)	0.39
Radiologic hip OA (KL ≥ 2)	3.2 (-2.2 to 8.6)	0.24	**6.6 (0.7 to 12.5)**	**0.03**
Treatment (placebo)	-2.9 (-7.9 to 2.1)	0.25	-2.0 (-7.4 to 3.5)	0.48
LoguCTX-II (pg/umol creat)	2.6 (-1.9 to 7.1)	0.26	4.3 (-1.2 to 9.9)	0.13
LoguCIIM (pg/umol creat)	-1.6 (-5.7 to 2.5)	0.44	-0.7 (-5.8 to 4.3)	0.77

uCTX-II = C-terminal telopeptides of type II collagen, uCIIM = type II collagenmarker, creat = creatinine, CI = confidence interval, bold figures indicate p<0.05. The coefficient indicates the magnitude of change in pain score expected from a 1-unit change in the variable

Table 2b Results of multivariate linear mixed model analysis of biochemical markers and symptom severity during 2 years of follow-up with 6-monthly measurements; subgroup of patients with minimal radiologic hip OA (KL<2).

Variable	WOMAC pain (0-100) (n=114)		VAS pain (0-100) (n=114)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Gender (female)	**11.5 (2.2 to 20.8)**	**0.02**	**12.6 (2.4 to 22.8)**	**0.02**
Age (years)	0.2 (-0.3 to 0.7)	0.35	0.3 (-0.2 to 0.9)	0.21
Body mass index (kg/m^2)	**1.2 (0.4 to 1.9)**	**<0.01**	**1.2 (0.3 to 2.0)**	**<0.01**
Duration of complaints (>3 year)	3.2 (-4.1 to 10.5)	0.39	5.7 (-2.4 to 13.7)	0.17
Concomitant knee OA	1.7 (-7.1 to 10.5)	0.71	-1.7 (-11.3 to 8.0)	0.73
Concomitant hand OA	-4.2 (-12.2 to 3.8)	0.30	-6.2 (-25.0 to 2.5)	0.16
Treatment (placebo)	-0.7 (-8.0 to 6.7)	0.85	0.4 (-7.6 to 8.5)	0.91
LoguCTX-II (pg/umol creat)	1.3 (-4.0 to 6.4)	0.63	-3.4 (-9.9 to 3.0)	0.30
LoguCIIM (pg/umol creat)	-2.0 (-7.4 to 3.4)	0.46	4.8 (-1.6 to 11.3)	0.14

uCTX-II = C-terminal telopeptides of type II collagen, uCIIM = type II collagen marker, creat = creatinine, CI = confidence interval, bold figures indicate p<0.05.

Table 2c Results of multivariate linear mixed model analysis of biochemical markers and symptom severity during 2 years of follow-up with 6-monthly measurements; subgroup of patients with definite radiologic hip OA (KL≥2).

Variable	WOMAC pain (0-100) (n=108)		VAS pain (0-100) (n=108)	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Gender (female)	5.8 (-1.7 to 13.3)	0.13	3.0 (-5.0 to 11.1)	0.46
Age (years)	-0.1 (-0.5 to 0.3)	0.67	-0.1 (-0.6 to 0.3)	0.54
Body mass index (kg/m2)	0.6 (-0.3 to 1.4)	0.20	**1.0 (0.1 to 1.9)**	**0.03**
Duration of complaints (>3 year)	**10.7 (3.3 to 18.0)**	**<0.01**	**9.7 (1.8 to 17.6)**	**0.02**
Concomitant knee OA	1.9 (-6.0 to 9.9)	0.63	-1.7 (-10.1 to 6.7)	0.70
Concomitant hand OA	-2.2 (-10.5 to 6.2)	0.61	2.2 (-6.8 to 11.1)	0.63
Treatment (placebo)	-6.7 (-13.8 to 0.4)	0.06	-5.8 (-13.4 to 1.8)	0.13
LoguCTX-II (pg/umol creat)	6.0 (-1.8 to 13.8)	0.13	**17.1 (7.7 to 26.5)**	**<0.01**
LoguCIIM (pg/umol creat)	-0.4 (-6.7 to 5.8)	0.90	-6.3 (-14.1 to 1.5)	0.12

uCTX-II = C-terminal telopeptides of type II collagen, uCIIM = type II collagen marker, creat = creatinine, CI = confidence interval, bold figures indicate p<0.05

Multinomial regression analysis showed that, compared to patients in the mild pain trajectory, patients in the highly progressive pain trajectory were more likely to have a higher loguCTX-II (OR 6.7; 95% CI 1.6-28.2) at baseline (Table 3). The odds ratio (OR) for loguCTX-II was higher than that for the duration of complaints or severity of radiologic OA. Patients in the moderate pain trajectory were also more likely to have a higher loguCTX-II at baseline (OR 4.8; 95% CI 1.0-22.8) compared to the mild pain trajectory.

After adjustment for the imaging marker (radiologic OA), patients in the highly progressive pain trajectory were more likely to have a higher loguCTX-II (OR 4.6; 95% CI 1.0-19.9; p 0.04) at baseline. LoguCTX-II explained 5% of the variance of the model and loguCIIM explained 1% of the variance (Table 3).

Table 3 Multinomial binary regression analysis for individual baseline variables for the four trajectories of hip pain (mild hip pain trajectory was used as reference group).

	Moderate pain		Always pain		Regularly progressive pain traject		Highly progressive pain traject		explained variance by model
	n=31		n=32		n=48		n=42		
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	
Gender (female)	2.1	0.8 - 5.5	2.2	0.8 - 5.7	1.2	0.6 - 2.6	1.5	0.7 - 3.5	2%
Duration of hip complaints (≥3 years)	1.8	0.8 - 4.2	**3.2**	**1.3 - 7.8**	1.6	0.8 - 3.3	**2.6**	**1.2 - 5.8**	5%
Concomitant knee OA	2.3	0.9 - 6.0	2.5	1.0 - 6.5	**3.4**	**1.5 - 7.9**	**2.6**	**1.1 - 6.4**	5%
Concomitant hand OA	0.8	0.4 - 2.0	1.5	0.6 - 3.5	1.8	0.8 - 3.7	1.5	0.7 - 3.3	2%
Radiologic hip OA (KL ≥ 2)	1.9	0.8 - 4.4	**3.3**	**1.4 - 8.0**	2.0	0.9 - 4.3	**3.3**	**1.5 - 7.2**	6%
Age	1.0	0.9 - 1.0	1.0	1.0 - 1.1	1.0	1.0 - 1.1	1.0	1.0 - 1.1	2%
Body Mass Index*	**1.1**	**1.0 - 1.3**	**1.2**	**1.1 - 1.4**	**1.1**	**1.0 - 1.2**	**1.2**	**1.1 - 1.3**	9%
LoguCTX-II pg/umol creat**	**4.8**	**1.0 - 22.8**	4.1	0.9 -19.5	1.5	0.5 - 5.1	**6.7**	**1.6 - 28.2**	5%
LoguCIIM pg/umol creat**	2.3	0.5 - 11.9	1.5	0.3 - 7.4	0.9	0.2 - 3.4	1.7	0.4 - 7.2	1%

uCTX-II = C-terminal telopeptides of type II collagen, uCIIM = type II collagen marker, creat = creatinine, * n=220, ** n=197, **bold** figures indicate p<0.05.

Discussion

In patients with mild-moderate hip OA, urinary CTX-II and CIIM were not cross-sectionally associated with patients' perceived severity of hip pain (measured with WOMAC pain and VAS pain) over the 2-year follow-up. Patients in the moderate pain trajectory and in the highly progressive pain trajectory were more likely to have a higher loguCTX-II at baseline than patients in the mild pain trajectory.

Results of earlier studies on the relationship between uCTX-II and patients' perceived pain are conflicting. One cross-sectional study in patients with knee OA showed no association between uCTX-II and WOMAC total score, and uCTX-II and WOMAC pain score.[17] However, another study in patients with knee OA suggested that patients with a high level of uCTX-II at baseline have a significant correlation with WOMAC scores, with a peak at 18-months follow-up.[18] In hip OA the correlation between uCTX-II and pain has also been shown to be cross-sectional.[4]

Urinary CIIM has not been investigated as extensively as uCTX-II. Although serum CIIM levels are reported to be higher in patients with radiographic knee OA than in those without radiographic knee OA, its relationship with pain has not previously been investigated.[6] Serum CIIM levels are reported to be somewhat predictive for structural progression in ankylosing spondylitis[19] and for treatment response in rheumatoid arthritis.[20]

Although both CTX-II and CIIM are neoepitopes of type II collagen, clear histological differences have been observed which may explain differences in results between the two markers. CTX-II seems to be released from the eroded and fibrillated surface of the OA cartilage as well as the interface between the subchondral bone and the calcified cartilage.[21] In contrast, CIIM seems to be released from the articular cartilage.[6] In other words, CTX-II may be associated to a greater extent with the innervated bone tissue, whereas CIIM may be uniquely derived from the non-innervated articular cartilage. In our data uCIIM and uCTX-II were not correlated to each other.

The relationship between uCTX-II and radiographic OA has been reported previously in both knee and hip OA in cross-sectional designs.[4, 7, 22] Moreover, Reijman et al. showed that in patients with hip pain, the association between uCTX-II levels and radiographic OA was stronger (OR 20.4) than in patients without hip pain (OR 3.0).[7]

A strength of our study is the longitudinal design with five repeated follow-up measurements of urinary biomarkers and pain scores during 2-year follow-up; this allowed to explore the relationship between biomarkers and pain over time. Although cross-sectional associations between biomarkers and clinical outcomes have previously been reported, longitudinal associations have not yet been extensively investigated. For clinical use, it would be interesting to have biomarkers that are associated with future clinical outcomes of OA over a longer follow-up period. Then these biomarkers could be used to monitor disease progression or treatment effects over time. Another strength is that in our linear mixed models we were able to correct for some well-known covariables such as age, BMI and severity of radiologic hip OA.

The study also has some limitations. The first is that although we have information on knee OA and hand OA, we do not know whether knee OA or hand OA was unilateral of bilateral.

Urinary CTX-II and uCIIM are not specific markers for the hip, but are released in every joint. Therefore, it would be interesting to see whether the results are different when a weighted adjustment could be done, counting the number of joints affected by OA. In addition, it would also be interesting to adjust for lower back OA, since an association has been shown between CTXII and disc space narrowing.[23]

Another possible limitation is the use of glucosamine in half of the patients. Although the results of the GOAL trial showed that clinical symptoms and radiographic progression of hip OA did not differ between active treatment and placebo at any follow-up measurement,[9] other studies reported that glucosamine administration significantly decreased uCTX-II levels.[24] Therefore, a possible effect of glucosamine on uCTX-II levels cannot be ruled out. However, because analyses with and without adjustment for treatment yielded the same results, we believe that the contribution of a possible effect of glucosamine to the model is small.

In addition, we had no information on the menopausal status of the included women. This might have influenced the results, as it is reported that postmenopausal women show higher

levels of uCTXII than premenopausal women.[25] However, we believe that this would have little influence in the present study because the mean age of our population was 63 years (an age when most women have reached menopausal status). To further study the possible effect of the menopausal status, we analyzed men and women separately. In both groups no association was found between uCTX-II or uCIIM and severity of hip pain.

The GOAL study recruited prevalent cases of patients registered with hip OA or patients with symptoms associated with hip OA in the medical records of the general practices. These patients were contacted by their general practitioner (GP) and informed about the study. However, because a selection of patients might have responded to the GP's invitation, there is a possibility of selection bias. Also, our results cannot be generalized to patients referred to secondary care for complaints of hip OA.

Finally, the results for the prediction of the course of pain were only analyzed bivariately because the numbers of patients in the five pain trajectories were too small to perform multivariate analysis. A larger patient population would allow exploring the association between uCTX-II and progressive pain related to other variables such as BMI and duration of complaints to see whether some of the covariates could be confounders. It would also show whether uCTX-II has an additional value to predictors that are easily assessed during history taking and physical examination.

Implications for clinical practice and research

During the 2-year follow-up, no cross-sectional association was found between uCTX-II or uCIIM and severity of hip pain in patients with clinical hip OA according to the ACR criteria registered in the medical records of general practices. Baseline uCTX-II was related to progressive pain trajectories during follow-up. Therefore, uCTX-II might help to identify patients at risk for a progressive pain trajectory. However, this needs further investigation and, although uCTX-II is commercially available, its value for the prognosis of an individual patient remains unclear. Further studies should also examine whether uCTX-II is a better predictor than other variables that are easier to assess by the GP (e.g., duration of complaints, gender), or variables already widely used in clinical practice (e.g., X-ray).

Based on this current work, we cannot recommend CIIM as a biomarker in hip OA in clinical practice.

Conclusion

This study shows that, over a 2-year period, the urinary biochemical markers uCTX-II and uCIIM were not cross-sectionally associated with perceived hip pain of patients with hip OA. However, uCTX-II might be helpful to estimate a progressive pain trajectory or a moderate pain trajectory over a 2-year period. This needs further evaluation in studies with a larger sample size.

References

1. Mobasheri A. Osteoarthritis year 2012 in review: biomarkers. Osteoarthritis Cartilage 2012; 20: 1451-1464.
2. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharm & Ther 2001; 69.
3. Rousseau J, Garnero P. Biological markers in osteoarthritis. Bone 2012; 51: 265-277.
4. Garnero P, Mazieres B, Gueguen A, Abbal M, Berdah L, Lequesne M, et al. Cross-sectional association of 10 molecular markers of bone, cartilage, and synovium with disease activity and radiological joint damage in patients with hip osteoarthritis: the ECHODIAH cohort. J Rheumatol 2005; 32: 697-703.
5. van Spil WE, DeGroot J, Lems WF, Oostveen JC, Lafeber FP. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. Osteoarthritis Cartilage 2010; 18: 605-612.
6. Bay-Jensen AC, Liu Q, Byrjalsen I, Li Y, Wang J, Pedersen C, et al. Enzyme-linked immunosorbent assay (ELISAs) for metalloproteinase derived type II collagen neoepitope, CIIM--increased serum CIIM in subjects with severe radiographic osteoarthritis. Clin Biochem 2011; 44: 423-429.
7. Reijman M, Hazes JM, Bierma-Zeinstra SM, Koes BW, Christgau S, Christiansen C, et al. A new marker for osteoarthritis: cross-sectional and longitudinal approach. Arthritis Rheum 2004; 50: 2471-2478.
8. Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis 2012; 71: 1517-1523.
9. Rozendaal RM, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. Ann Intern Med 2008; 148: 268-277.
10. Rozendaal RM, Koes BW, Weinans H, Uitterlinden EJ, van Osch GJ, Ginai AZ, et al. The effect of glucosamine sulphate on osteoarthritis: design of a long-term randomised clinical trial [ISRCTN54513166]. BMC Musculoskelet Disord 2005; 6: 20.
11. Rozendaal RM, Uitterlinden EJ, van Osch GJ, Garling EH, Willemsen SP, Ginai AZ, et al. Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial. Osteoarthritis Cartilage 2009; 17: 427-432.
12. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.
13. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494-502.
14. Bay-Jensen AC, Leeming DJ, Kleyer A, Veidal SS, Schett G, Karsdal MA. Ankylosing spondylitis is characterized by an increased turnover of several different metalloproteinase-derived collagen species: a cross-sectional study. Rheumatology international 2012; 32: 3565-3572.
15. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-1840.
16. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC medical research methodology 2008; 8: 70.

17. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E. Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. Ann Rheum Dis 2001; 60: 619-626.
18. Christgau S, Henrotin Y, Tanko LB, Rovati LC, Collette J, Bruyere O, et al. Osteoarthritic patients with high cartilage turnover show increased responsiveness to the cartilage protecting effects of glucosamine sulphate. Clin Exp Rheumatol 2004; 22: 36-42.
19. Bay-Jensen AC, Wichuk S, Byrjalsen I, Leeming DJ, Morency N, Christiansen C, et al. Circulating protein fragments of cartilage and connective tissue degradation are diagnostic and prognostic markers of rheumatoid arthritis and ankylosing spondylitis. PloS one 2013; 8: e54504.
20. Bay-Jensen AC, Platt A, Byrjalsen I, Vergnoud P, Christiansen C, Karsdal MA. Effect of tocilizumab combined with methotrexate on circulating biomarkers of synovium, cartilage, and bone in the LITHE study. Semin Arthritis Rheum 2014; 43: 470-478.
21. Bay-Jensen AC, Andersen TL, Charni-Ben Tabassi N, Kristensen PW, Kjaersgaard-Andersen P, Sandell L, et al. Biochemical markers of type II collagen breakdown and synthesis are positioned at specific sites in human osteoarthritic knee cartilage. Osteoarthritis Cartilage 2008; 16: 615-623.
22. Jordan KM, Syddall HE, Garnero P, Gineyts E, Dennison EM, Sayer AA, et al. Urinary CTX-II and glucosyl-galactosyl-pyridinoline are associated with the presence and severity of radiographic knee osteoarthritis in men. Ann Rheum Dis 2006; 65: 871-877.
23. Goode AP, Marshall SW, Kraus VB, Renner JB, Sturmer T, Carey TS, et al. Association between serum and urine biomarkers and lumbar spine individual radiographic features: the Johnston County Osteoarthritis Project. Osteoarthritis Cartilage 2012; 20: 1286-1293.
24. Yoshimura M, Sakamoto K, Tsuruta A, Yamamoto T, Ishida K, Yamaguchi H, et al. Evaluation of the effect of glucosamine administration on biomarkers for cartilage and bone metabolism in soccer players. Int J Mol Med 2009; 24: 487-494.
25. van Spil WE, Jansen NW, Bijlsma JW, Reijman M, DeGroot J, Welsing PM, et al. Clusters within a wide spectrum of biochemical markers for osteoarthritis: data from CHECK, a large cohort of individuals with very early symptomatic osteoarthritis. Osteoarthritis Cartilage 2012; 20: 745-754.

CHAPTER 6

Associations between weather conditions and clinical symptoms in patients with hip osteoarthritis: A 2-year cohort study

DMJ Dorleijn, PAJ Luijsterburg, A Burdorf, RM Rozendaal, JAN Verhaar, PK Bos, SMA Bierma-Zeinstra

Pain 2014, Apr 155 (4) 808–813

Abstract

Objectives: The goal of this study was to assess whether there is an association between ambient weather conditions and patients' clinical symptoms in patients with hip osteoarthritis (OA).

Methods: The design was a cohort study with a 2-year follow-up and 3-monthly measurements and prospectively collected data on weather variables. The study population consisted of 222 primary care patients with hip OA. Weather variables included temperature, wind speed, total amount of sun hours, precipitation, barometric pressure, and relative humidity. The primary outcomes were severity of hip pain and hip disability as measured with the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) pain and function subscales. Associations between hip pain and hip disability and the weather variables were assessed using crude and multivariate adjusted linear mixed-model analysis for repeated measurements.

Results: On the day of questionnaire completion, mean relative humidity was associated with WOMAC pain (estimate 0.1; 95% confidence interval 0.0–0.2; p 0.02). Relative humidity contributed <1% to the explained within-patient variance and between-patient variance of the WOMAC pain score. Mean barometric pressure was associated with WOMAC function (estimate 0.1; 95% confidence interval 0.0–0.1; p 0.02). Barometric pressure contributed <1% to the explained within-patient variance and between-patient variance of the WOMAC function score. The other weather variables were not associated with the WOMAC pain or function score.

Conclusion: Our results support the general opinion of OA patients that barometric pressure and relative humidity influence perceived OA symptoms. However, the contribution of these weather variables (<1%) to the severity of OA symptoms is not considered to be clinically relevant.

Introduction

Patients with osteoarthritis (OA) often report that weather conditions (such as precipitation and temperature) influence their clinical symptoms such as pain and joint stiffness.[1] Up to 62% of OA patients believe that they are weather sensitive and that, for example, temperature and precipitation aggravate their OA symptoms.[2]

Systematically searching the literature (PubMed, Embase, and the Cochrane Library from 1966 until July 2012) on associations between weather conditions and OA yielded 11 articles describing 11 studies (Appendices A and B).

Patients included in these studies were diagnosed with rheumatoid arthritis (RA) or OA. The joints involved in OA were specified in 4 studies.[3-6] Although all these studies had a prospective design, only 3 covered all seasons of the year.[6-8] None of the meteorological variables showed a consistent correlation with patients' pain in OA. An increase in temperature was correlated with a decrease in pain in 4 studies and with an increase in pain in 1 study, and was not correlated with pain in 5 studies. An increase in barometric pressure was correlated with a decrease in pain in 1 study and an increase in pain in 6 studies, and was not correlated with pain in 4 studies. Precipitation and relative humidity were positively correlated with pain in 3 studies and not correlated with pain in 5 studies (precipitation) and 6 studies (relative humidity). These differences could be caused by differences in the data collection. Some studies assessed pain and weather variables multiple times per day and used all of these measurements as different data points.[7] Others used the average of weather variables over 24 hours.[2, 5] The studies also used different techniques for analysis, varying from simple correlation to mixed model analysis.[5, 8] (see Appendix C for details on the characteristics of all 11 studies) Thus, studies have been unable to provide consistent evidence for a relationship between OA symptoms and weather conditions.[1, 3, 5-7, 9-11]

The present study investigates whether there is an association between ambient weather conditions (e.g. precipitation, temperature, barometric pressure) and patients' hip pain and hip function, in primary care patients with hip OA. For this, we used a large prospective cohort study with 3-monthly measurements over 2 years of follow-up, with validated functional scoring systems and data of weather variables at all data points.

Methods

STROBE recommendations

When executing the study, the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) were followed.[12]

Study population

The study population consisted of primary care patients diagnosed with hip OA (n = 222) who participated in a prospective, randomized, controlled trial that assessed the effect of glucosamine sulphate (the GOAL trial: *glucosamine sulphate in hip osteoarthritis*).[13-15] The Medical Ethics Committee of the Erasmus MC approved the study design, and all patients provided written informed consent. This trial recruited patients with hip complaints from general practices in the Rotterdam area of the Netherlands. All patients were residing in the Rotterdam area. Patients were eligible if they met the clinical and/or radiological American College of Rheumatology criteria for hip OA.[16] Patients who had undergone or were awaiting total hip replacement (THR) surgery and patients with a Kellgren & Lawrence (KL) score of 4 were excluded.[17]

Patients were also excluded if they had renal disease, liver disease, or diabetes mellitus, or were already taking glucosamine. Also excluded were patients with a disabling comorbid disease that would make a visit to the research center impossible, and those unable to complete questionnaires in the Dutch language. Patients were assessed every 3 months during a 2-year follow-up.

We considered the 222 participants as 1 cohort because the results of the GOAL trial showed that clinical symptoms and radiographic progression of hip OA did not differ between active treatment and placebo at any follow-up measurement.[13]

Clinical outcomes

The outcomes were severity of hip pain and hip function reported by the patient. These were assessed with a validated measuring instrument: the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) subscale for hip pain and subscale for function.[18] The WOMAC subscales were converted to a score of 0 to 100, in which 0 indicated no pain or no disability. The WOMAC is recommended by the Osteoarthritis Research Society International for use in clinical trials in patients with hip OA to assess pain and disability.[18] In the WOMAC questionnaire, a self-administered questionnaire, patients' symptoms during the last 2 days were scored. If patients had a THR during follow-up, available data were included in the analysis until surgery; data collected after surgery were not used in the analysis.

Patients filled in a questionnaire, which included the WOMAC questionnaire, every 3 months. The baseline questionnaire and the 2-year questionnaire were completed at the research centre; the other 7 questionnaires were completed at home and sent to the researchers by mail. This resulted in 9 recordings per patient in total (1 at baseline and 8 during follow-up). The date of completion was reported; however, the time of the day on completion of the questionnaire was unknown.

Weather variables

Weather variables of the patients' residences (weather station Rotterdam) were retrieved from the Royal Netherlands Meteorological Institute[19] and included the following: mean temperature (in degrees Celsius), mean wind speed (in meters/s), total amount of sun hours, total amount of precipitation (in millimeters), mean barometric pressure (hPa), and mean relative humidity (%).These variables were collected for the day of questionnaire completion of each patient.

Statistical analysis

Crude and adjusted linear mixed-model analysis for repeated measurements were used to assess associations between patients' severity of hip pain and hip joint disability and the weather variables of interest. This technique adjusts for the within-patient correlation for the outcomes in each patient and uses each outcome from each patient as a separate observation.

In the mixed-model analyses, the weather variables were included as fixed factors. The compound structured covariance structure was used, assuming that the within-subject and between-subject variance is a constant. Weather variables that showed a significance level of $p < 0.15$ with the outcome in the binary linear mixed-model analysis were entered in the multivariate, adjusted linear mixed-model analysis. Covariates that were associated with 1 of the outcomes (WOMAC function or WOMAC pain; $p < 0.15$) in the binary analysis were included in the adjusted models as fixed factors to be adjusted for.

We were also interested in whether associations between weather variables and hip OA were more prominent in patients with definite radiologic hip OA (KL≥2) versus patients with early radiologic OA (KL< 2). Therefore, a subgroup analysis was performed for patients with a KL score of 2/3. Between-patient and within-patient variances were calculated for the intercept-only model, the crude model, and the multivariate adjusted model. All analyses were performed using SPSS version 20.0.

Results

Study population

A total of 222 patients participated in the GOAL trial; Table 1 shows the baseline characteristics of these patients. The mean age was 63.4 years (standard deviation [SD] 9.0 years), and 69.4% of patients were female. At baseline, the mean WOMAC pain score was 34.2 (SD 23.1), and the mean WOMAC function score was 35.1 (SD 22.9). Because of patients undergoing a THR during the 2-year follow-up and patients lost to follow-up, the number of patients with available data ranged from 217 patients (98%) at the 3-month follow-up to 188 patients (84.7%) at the 2-year follow-up.[13]

Table 1 Baseline characteristics of the 222 primary care patients with hip OA.

Characteristic		Patients (n=222)
Gender	Female	154 (69.4)
Age in years		63.4 (9.0)
Body mass index (kg/m^2)		28.0 (4.7)
Duration of complaints	<1 year	26 (11.7)
	1-3 years	77 (34.7)
	>3 years	119 (53.6)
OA	Localised*	85 (38.3)
	Generalised	137 (61.7)
Radiologic hip OA	KL 1	114 (51.4)
KL ≥ 2	108 (48.6)	
Pain medication users		112 (50.5)
WOMAC pain (0-100)		34.2 (23.1)
WOMAC function (0-100)		35.1 (22.9)
WOMAC stiffness (0-100)		42.6 (25.2)
VAS hip pain (0-100)		32.4 (25.9)

Categorical data are presented as number (%); continuous data as mean (standard deviation) KL = Kellgren & Lawrence grading of radiologic OA; OA = Osteoarthritis; VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities. * Localised = only hip OA; Generalised = OA in hips, hands and/or knees

Clinical outcomes

The mean WOMAC subscores showed little variation over the study period. The WOMAC pain score decreased from 34.2 (SD 23.1) at baseline to 32.1 (SD 23.5) at 2-year follow-up. The WOMAC function score improved from 35.1 (SD 22.9) at baseline to 33.3 (SD 23.8) at 2-year follow-up.

Weather

On the days of questionnaire completion, the mean barometric pressure was 1016.1 (SD 9.6) hPa and the mean relative humidity was 82.5% (SD 7.6). The range of barometric pressure was 980.4 to 1041.7, and the range of relative humidity was 49% to 99%. The mean temperature was 10.1°C (SD 6.1°C). The median wind speed was 3.9 m/s (25%–75% interquartile range [IQR] 2.8–5.5 m/s), and the median precipitation was 0.1 mm (25%–75% IQR 0.0–2.4 mm). The median hours of sun per day were 3.8 (25%–75% IQR 1.1–7.5).

Associations among clinical outcomes, individual characteristics, disease aspects, and weather

The results of the binary linear mixed model analysis on the day of questionnaire completion are presented in Table 2. Six covariates were associated ($p < 0.15$) with WOMAC pain and/or

WOMAC function: gender, body mass index (BMI), duration of OA complaints, localised versus generalised OA, unilateral versus bilateral OA, and severity of radiologic OA (KL 1 vs KL≥2). Relative humidity was associated with WOMAC pain (estimate 0.1; 95% confidence interval [CI] 0.0–0.2), and barometric pressure was associated with WOMAC function (estimate 0.1; 95% CI 0.0–0.1).

Table 2 Results of binary linear mixed model analysis of weather variables and clinical outcomes on the day of questionnaire completion during 2 years of follow-up with 3-monthly measurements.

Variable	WOMAC pain (0-100)		WOMAC function (0-100)	
	Estimate* (95% CI)	p value	Estimate (95% CI)	p value
Gender (female)	8.8 (3.3 to 14.4)	<0.01	6.8 (0.7 to 12.8)	0.03
Body mass index (kg/m^2)	1.3 (0.7 to 1.8)	<0.01	1.6 (1.0 to 2.2)	<0.01
Duration of complaints				
< 6 months	-22.6 (-35.5 to -9.7)	<0.01	-20.6 (-34.6 to -6.5)	<0.01
6 to 12 months	-3.3 (-13.1 to 6.5)	0.51	-6.0 (-16.7 to 4.6)	0.27
1 to 3 years	-7.7 (-13.2 to -2.1)	<0.01	-9.1 (-15.1 to -3.1)	<0.01
>3 years	reference		reference	
Localised vs generalised OA (localised)	-4.5 (-9.8 to 0.8)	0.10	-6.3 (-12.0 to -0..5)	0.03
Severity radiologic OA (KL< 2)	-3.8 (-9.1 to 1.3)	0.14	-7.3 (-12.9 to -1.8)	0.01
Unilateral vs bilateral OA (unilateral)	-3.7 (-8.9 to 1.5)	0.16	-5.5 (-11.1 to 0.1)	0.06
Precipitation (mm)	0.0 (-0.1 to 0.1)	0.89	-0.1 (-0.2 to 0.0)	0.15
Sun hours (per day)	-0.1 (-0.3 to 0.1)	0.27	-0.0 (-0.1 to 0.1)	0.88
Temperature (degrees Celsius)	0.0 (-0.1 to 0.1)	0.84	-0.0 (-0.1 to 0.1)	0.61
Wind speed (m/sec)	-0.2 (-0.5 to 0.1)	0.19	-0.2 (-0.5 to 0.0)	0.09
Barometric pressure (hPa)	0.0 (-0.0 to 0.1)	0.51	0.1 (0.0 to 0.1)	<0.01
Relative humidity (%)	0.1 (0.0 to 0.2)	0.03	0.0 (-0.0 to 0.1)	0.16

CI = confidence interval; OA = osteoarthritis; SD = standard deviation: WOMAC = Western Ontario and McMaster Universities. * Estimate indicates the magnitude of change in pain or function score expected from a 1-unit change in the variable of interest.

In the multivariate adjusted mixed-model analysis, relative humidity was associated with WOMAC pain (estimate 0.1; 95% CI 0.0–0.2), and barometric pressure was associated with WOMAC function (estimate 0.1; 95% CI 0.0–0.1) (Table 3).

The estimate indicates the magnitude of change in pain score or function score expected from a 1-unit change in the weather variable. Thus, for each increase of 10% in relative humidity, the WOMAC pain score increased by 1.0 on a scale of 0 to 100. For each 10-hPA increase in barometric pressure, the WOMAC function score deteriorated by 1.0 point (scale, 0–100). In a sensitivity subgroup analysis performed in patients with a KL score of 2/3, similar results were found.

Table 3 Results of multivariate adjusted linear mixed model analysis of weather variables and clinical outcomes on the day of questionnaire completion during 2 years of follow-up with 3-monthly measurements.

Variable	WOMAC pain (0-100)		WOMAC function (0-100)	
	Estimate (95% CI)	p value	Estimate (95% CI)	p value
Gender (female)	7.3 (1.8 to 12.8)	0.01	5.2 (-0.6 to 11.0)	0.08
Body mass index (kg/m^2)	1.1 (0.5 to 1.6)	<0.01	1.4 (0.8 to 2.0)	<0.01
Duration of complaints				
< 6 months	-20.2 (-32.6 to -7.9)	<0.01	-18.0 (-31.0 to -4.9)	<0.01
6 to 12 months	-2.2 (-11.8 to 7.3)	0.65	-5.1 (-15.2 to 5.0)	0.32
1 to 3 years	-6.1 (-11.4 to -0.7)	0.03	-6.5 (-12.2 to -0.9)	0.02
> 3 years	reference		reference	
Localised vs generalised OA (localised)	-1.8 (-7.8 to 3.4)	0.49	-2.8 (-8.2 to 2.7)	0.32
Severity radiologic OA (KL<2)	-4.4 (-9.6 to 0.7)	0.09	-6.8 (-12.3 to -1.4)	0.02
Unilateral vs bilateral OA (unilateral)	-2.2 (-7.1 to 2.6)	0.37	-3.7 (-8.8 to 1.5)	0.16
Relative humidity (%)	0.1 (0.0 to 0.2)	0.02	not included in model	
Wind speed (m/sec)	not included in model		-0.1 (-0.4 to 0.2)	0.42
Barometric pressure (hPa)	not included in model		0.1 (0.0 to 0.1)	0.02

CI = confidence interval; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities. * Estimate indicates the magnitude of change in pain or function score expected from a 1-unit change in the weather variable.

Table 4 shows the between-patient and within-patient variances for WOMAC function regarding barometric pressure and for WOMAC pain regarding relative humidity. Barometric pressure contributed <1% to the explained within-patient and between-patient variance of the WOMAC function score. Also, relative humidity contributed 61% to the explained within-patient and between-patient variance of the WOMAC pain score.

Additional analysis

In an additional analysis, we calculated the means of the weather variables for the 2 days preceding the day of questionnaire completion, and analysed whether these means of weather variables were associated with WOMAC pain and/or WOMAC function. In the adjusted linear mixed-model analysis, only average precipitation over the 2 days preceding the day of questionnaire completion was associated with WOMAC function (estimate-0.2; 95% CI -0.3 to -0.0; p 0.02). This indicates that for each 10-mm average increase in precipitation in the 2 days preceding questionnaire completion, the WOMAC function (scale, 0–100) improved by 2 points.

Table 4 Patient variances for WOMAC pain and relative humidity, and for WOMAC function and barometric pressure.

Variable	WOMAC function		WOMAC pain	
	bP (% explained)	wP (% explained)	bP (% explained)	wP (% explained)
IC only	436	113	363	164
IC + barometric pressure	435 (<1)	112 (<1)	--	--
IC + relative humidity	--	--	363 (<1)	163 (<1)
IC + wind speed	436 (<1)	112 (<1)	--	--
IC + gender	428 (2)	--	348 (4)	--
IC + duration of OA	413 (5)	--	341 (6)	--
IC + BMI	387 (11)	--	333 (8)	--
IC + severity of radiologic OA	425 (3)	--	362 (<1)	--
IC + covariates	354 (19)	113 (<1)	303 (17)	164 (<1)
IC + covariates + wind speed + barometric pressure	352 (19)	112 (<1)	--	--
IC + covariates + relative humidity	--	--	304 (16)	164 (<1)

BMI = body mass index; bP = between patient variance; IC = intercept; OA = osteoarthritis; WOMAC = Western Ontario and McMaster Universities; wP = within patient variance. Covariates are gender, duration of OA, BMI, localised vs generalized OA, unilateral vs bilateral OA and severity of radiologic OA.

Discussion

This study shows that, in patients with hip OA, there was an association between relative humidity and patients' severity of hip pain (estimate 0.1; 95% CI 0.0–0.2) and between barometric pressure and patients' hip function (estimate 0.1; 95% CI 0.0–0.1). However, the contribution of these weather variables in the pain score or function score was small. An increase of 10% in relative humidity increased the WOMAC pain score by 1 on a scale of 0 to 100. In addition to this, the range of relative humidity in our database was 49% to 99%, which corresponds to a maximum change in pain score of 5 on a scale of 0 to100. Similarly, for each 10-hPa increase in barometric pressure, the WOMAC function score deteriorates by 1 point on a scale of 0 to 100. The range of barometric pressure in our database was 980.4 to 1041.7, resulting in a maximum change in function score of 6.1 on a scale of 0 to 100. Pham et al. defined a clinically relevant moderate improvement in pain or function as an absolute change of ≥10 in pain of function score on a scale of 0 to 100 or an improvement of 20% in pain or function score.[20] Our results for both WOMAC pain and WOMAC function are therefore not clinically relevant. Second, relative humidity and barometric pressure explained only a very small part (<1%) of the within-patient and between-patient variances of patients' severity of hip pain and hip function.

A possible cause of these small associations could be that weather data were measured very precisely, whereas the pain data were assessed on a less precise level. Another explanation could be that there is no relationship between weather and OA symptoms, but that people tend to perceive patterns. One study has shown that people believe that arthritis symptoms are related

to barometric pressure, temperature, or humidity, but the investigators found no correlations between these weather-related variables and pain, joint tenderness, or functional status.[21]

The underlying mechanism as to why weather variables could affect pain or disability on OA is not well understood. Several hypotheses have been formulated. Fluctuations in atmospheric pressure could lead to synovial fluid being forced into the subchondral bone, which can aggravate pain and disability. However, Brennan et al.[3] did not find evidence to support this in their study. A cadaver study by Wingstrand et al.[22] demonstrated that the stability of the hip is maintained primarily by atmospheric pressure. Changes in atmospheric pressure could change hip stability and lead to subluxation of the hip.

Strengths and limitations

Our study used a relatively large dataset of 222 hip OA patients whose symptoms were assessed with questionnaires every 3 months over a 2-year follow-up period. Therefore, we were able to include weather variables during all seasons of the year. As there is a clear 4-season climate in the Netherlands, we believe that this is an important strength of the study. Also, this study used an appropriate statistical method (linear mixed models) for analyzing the associations between weather and symptoms of hip OA.

This study also has some limitations. First, the weather variables were all averaged over 24 hours; it was not possible to retrieve the changes in weather variables for each hour of the 24 hours of the day. The change in a weather variable from hour to hour potentially could be of more importance to a patient's clinical symptoms than a daily average. Furthermore, as we were also unaware of the time of day that the questionnaire was completed, the influence of time of day could not be assessed in this study. In addition, because we did not have data on psychological variables in the patients, we were unable to examine or correct for psychological factors in our analysis. In addition, although up to 62% of patients with OA have been reported to believe that weather can change their OA symptoms,[2] we lacked information on our patients' weather sensitivity. Outcomes might differ between patients who believe that they are weather sensitive and patients who do not.

Another important point is the fact that we were unaware of the time that patients spent indoors and outdoors. Compared to outdoors, staying indoors could less affect people regarding temperature and precipitation. However, barometric pressure is a weather variable that remains equal indoors and outdoors.[9]

A final important point is the selection of the study population. Patients were excluded from the GOAL study if they had severe radiographic OA (KL 4). The effects of weather could be more troublesome to patients with severe OA than to patients with mild to moderate OA.

Comparison with literature

Our study shows that higher relative humidity is associated with more hip pain in OA patients. Although this is in accordance with 3 earlier studies, those studies included patients with OA,

RA, and knee OA, not only hip OA.[4, 7, 8] Six studies reported no correlation between humidity and OA.[1, 2, 5, 9-11] The contribution that our study makes to this accrued evidence is that the magnitude of this association is small and clinically not relevant.

Although the correlation between barometric pressure and OA is mainly positive in previous studies,[3-7, 10] the correlation between barometric pressure and hip function has been studied only once.[12] Verges et al. reported a significant correlation between humidity and functional incapacity as measured with the Health Assessment Questionnaire (odds ratio 0.99; 95% CI 0.98–0.99; p 0.037).[11] Because this outcome showed only a borderline change, the authors reported that the correlation could not be conclusive from a clinical point of view. Our study agrees with their conclusion that the association between barometric pressure and hip function, albeit significant, was small in magnitude and clinically not relevant.

Only 1 study reporting on knee OA and weather variables showed the magnitude of the associations; however, for both temperature and pressure changes, the magnitude of the associations was small.[5] This latter study also examined the change in weather variables between the day before each pain report and the actual day of the pain report. In the multivariate analysis, although barometric pressure was correlated with the WOMAC pain score, the magnitude of this association was small.[5]

In neuropathic rats, lowering barometric pressure in a pressure chamber, within the range of natural weather, results in more sensitivity to pain.[23] Perhaps patients with neuropathic pain are also more weather sensitive than other patients. In our study, we were unaware of whether patients had neuropathic pain.

Recall bias

In the WOMAC questionnaire, patients scored their symptoms during the previous 2 days. Therefore, we hypothesized that the means of the different weather variables of the 2 days preceding questionnaire completion would correlate with these WOMAC pain scores. However, no such correlation was found in our data; on the contrary, there was a small association between the WOMAC pain score and the means of the weather variables on the day of questionnaire completion. It is known that there is a recall bias in pain questionnaires that address the means of pain during a previous time period; patients tend to rate their mean pain higher if their recent pain level is high and lower if their recent pain level is low.[24] This phenomenon might explain the influence of weather on hip symptoms over a short period of time (1 day) but not over a longer period of time (≥2 days).

Conclusion

In conclusion, our results support the general opinion of OA patients that barometric pressure and relative humidity influence OA symptoms (pain and disability). However, the contribution of these weather variables to the severity of OA symptoms is not considered to be clinically relevant.

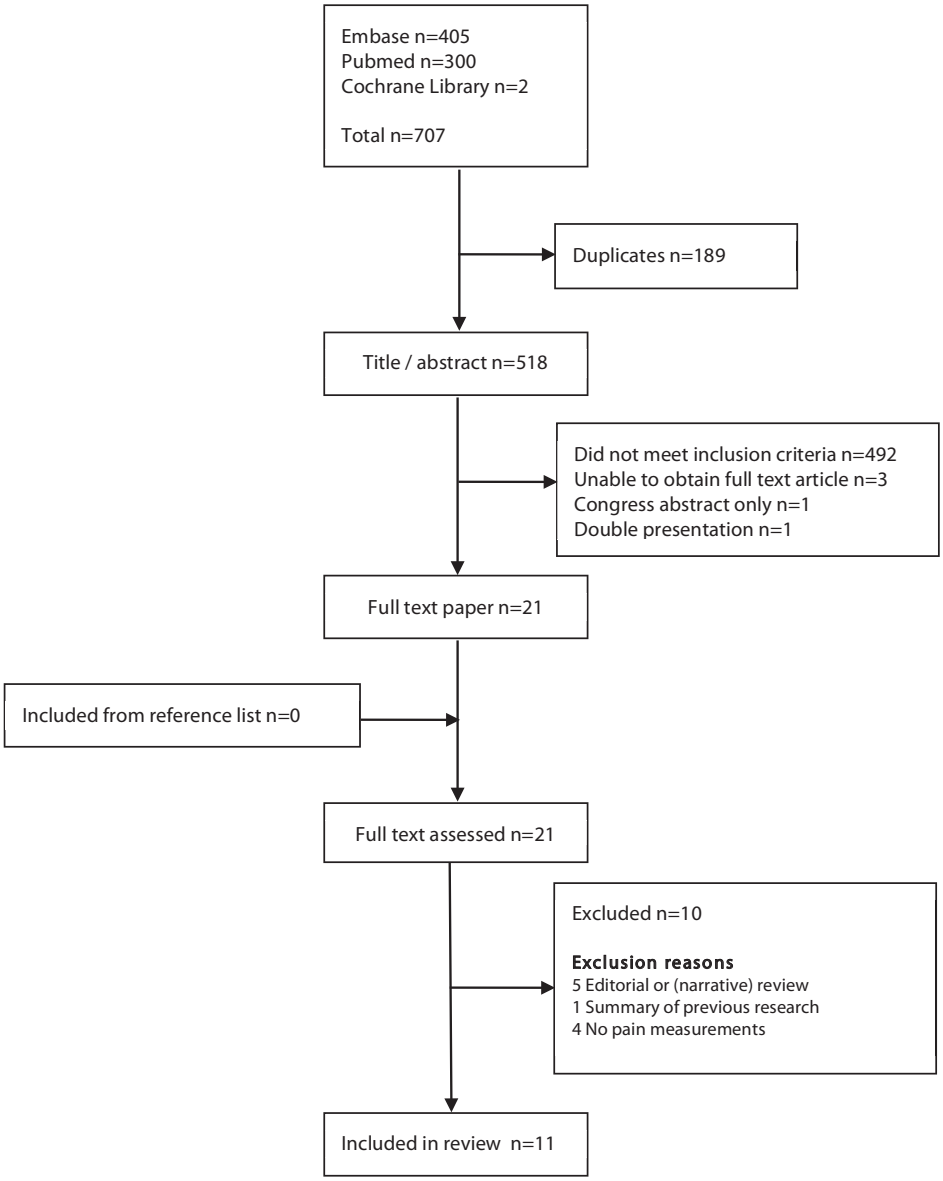
References

1. Laborde JM, Dando WA, Powers MJ. Influence of weather on osteoarthritics. Soc Sci Med 1986; 23: 549-554.
2. Sibley JT. Weather and arthritis symptoms. J Rheumatol 1985; 12: 707-710.
3. Brennan SA, Harney T, Queally JM, O'Connor McGoona J, Gormley IC, Shannon FJ. Influence of weather variables on pain severity in end-stage osteoarthritis. Int Orthop 2012; 36: 643-646.
4. Cay HF, Sezer I, Firat MZ, Kacar C. Which is the dominant factor for perception of rheumatic pain: meteorology or psychology? Rheumatol Int 2011; 31: 377-385.
5. McAlindon T, Formica M, Schmid CH, Fletcher J. Changes in barometric pressure and ambient temperature influence osteoarthritis pain. Am J Med 2007; 120: 429-434.
6. Wilder FV, Hall BJ, Barrett JP. Osteoarthritis pain and weather. Rheumatology 2003; 42: 955-958.
7. Aikman H. The association between arthritis and the weather. Int J Biometeorol 1997; 40: 192-199.
8. Strusberg I, Mendelberg RC, Serra HA, Strusberg AM. Influence of weather conditions on rheumatic pain. J Rheumatol 2002; 29: 335-338.
9. Clarke AM, Nicholl J. Does the weather affect the osteoarthritic patient? Br J Rheumatol 1991; 30: 477.
10. Guedj D, Weinberger A. Effect of weather conditions on rheumatic patients. Ann Rheum Dis 1990; 49: 158-159.
11. Verges J, Montell E, Tomas E, Cumelles G, Castaneda G, Marti N, et al. Weather conditions can influence rheumatic diseases. Proc West Pharmacol Soc 2004; 47: 134-136.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453-1457.
13. Rozendaal RM, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. Ann Intern Med 2008; 148: 268-277.
14. Rozendaal RM, Koes BW, Weinans H, Uitterlinden EJ, van Osch GJ, Ginai AZ, et al. The effect of glucosamine sulphate on osteoarthritis: design of a long-term randomised clinical trial [ISRCTN54513166]. BMC Musculoskelet Disord 2005; 6: 20.
15. Rozendaal RM, Uitterlinden EJ, van Osch GJ, Garling EH, Willemsen SP, Ginai AZ, et al. Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial. Osteoarthritis Cartilage 2009; 17: 427-432.
16. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.
17. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494-502.
18. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-1840.
19. Royal Netherlands Meteorological Institute. vol. 2011. Bilthoven.

20. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004; 12: 389-399.
21. Redelmeier DA, Tversky A. On the belief that arthritis pain is related to the weather. Proc Natl Acad Sci U S A 1996; 93: 2895-2896.
22. Wingstrand H, Wingstrand A, Krantz P. Intracapsular and atmospheric pressure in the dynamics and stability of the hip. A biomechanical study. Acta Orthop Scand 1990; 61: 231-235.
23. Funakubo M, Sato J, Obata K, Mizumura K. The rate and magnitude of atmospheric pressure change that aggravate pain-related behavior of nerve injured rats. Int J Biometeorol 2011; 55: 319-326.
24. Gendreau M, Hufford MR, Stone AA. Measuring clinical pain in chronic widespread pain: selected methodological issues. Best Pract Res Clin Rheumatol 2003; 17: 575-592.

Appendix A Search terms for articles reporting on OA and weather influences.

PubMed	(osteoarthritis[tw] OR (degenerative joint disease[tw])) AND (weather[tw] OR precipitation[tw] OR sunshine[tw] OR temperature[tw] OR (barometric pressure[tw]) OR (wind speed[tw]) OR (relative humidity[tw])) NOT (editorial[pt] OR letter[pt]) NOT (animals[mh] NOT humans[mh])
Embase	(osteoarthritis:de,ab,ti OR 'degenerative joint disease':de,ab,ti) AND (weather:de,ab,ti OR precipitation:de,ti,ab OR sunshine:de,ti,ab OR temperature:de,ti,ab OR 'barometric pressure':de,ti,ab OR 'wind speed':de,ti,ab OR 'relative humidity':de,ti,ab) NOT (editorial:pt OR letter:pt) NOT ([animals]/lim NOT [humans]/lim)
Cochrane	"osteoarthritis in Title, Abstract or Keywords and weather in Title, Abstract or Keywords in Cochrane Central Register of Controlled Trials"



Appendix B Study selection flow chart.

Appendix C Characteristics of studies reporting correlations between weather variables and pain in patients with OA.

Author; year	n	Diagnosis	Location	Analysis technique	Follow-up	n of observations	Meteorological variables and outcome					
						per patient	T	BP	RH	WS	P	S
Aikman 1997[7]	25	OA and/ or RA	Australia; New South Wales	Pearson's correlation coefficients; stepwise multiple regression	1 M every season	121 days; 4xD pain and weather	↓	↑	↑	↓	ns	NA
Brennan 2012[3]	53	hip OA	Ireland	Generalised linear mixed model	4 W	28 days; 1xD pain and weather	ns	↑	NA	NA	ns	NA
Cay 2011[4]	10	knee OA	Turkey	Spearman rank correlation; stepwise multiple regression	max. 6 M	1xD pain and weather	↓	↑	↑	ns	↑	↓
Clarke 1991[9]	53	OA	UK	Wilcoxon's matched pairs signed ranks test	30 D summer; 30 D winter	60 days, 1xD pain and weather	NA	ns	ns	NA	NA	NA
Guedj 1990[10]	24	OA	Israel	Chi square test; multiple regression analysis	4 W	28 days, 1xD pain and weather	↑	↑	ns	NA	↑	NA
Laborde 1986[1]	126	OA	USA; Illinois, North Dakota	Stepwise multiple regression	Cross sectional	1	ns	ns	ns	U: ↑; R:ns	U: ↑; R:ns	ns
McAlindon 2007[5]	200	knee OA	USA: several States	Longitudinal mixed model analysis	14 W (every 2W assessed)	9 days 1xD pain and weather	↓	↑	ns	NA	ns	NA
Sibley 1985[2]	35	OA	Canada; Saskatchewan	Wilcoxon rank sum test; Spearman rank correlation	1 M	28 days; 1xD pain and weather	ns	ns	ns	ns	ns	NA
Strusberg 2002[8]	52	OA	Argentina	Simple correlation	1 Y	365 days; 1xD pain; 4xD weather	↓	ns	↑	NA	NA	NA
Verges 2004[11]	80	OA	Spain	Binary regression	1 M	31 D; 1x/D pain and weather	ns	↓	ns	NA	NA	NA
Wilder 2003[6]	154	OA	USA; Florida	Generalised estimated equations	19 - 23 M	unknown	ns	↑*	NA	NA	ns	NA

OA=osteoarthritis, RA=rheumatoid arthritis, Y=year, M=Month(s), W= week(s), D=day(s), T=temperature, BP=barometric pressure, RH=relative humidity, WS=wind speed, P=precipitation, S=hours of sunshine, U= urban sample, R=rural sample, ↓ = negative correlation, ↑ =positive correlation, ns = not significant, NA=not assessed; * only women with hand OA (n=?; subpopulation of 154 patients), not neck, shoulder, knee or foot and not in men

CHAPTER 7

Greater trochanter pain syndrome: prevalence and influence on hip pain severity in patients with hip osteoarthritis in a cohort study

DMJ Dorleijn, PAJ Luijsterburg, A Brinks, RM Rozendaal, A Burdorf, BW Koes, JAN Verhaar, PK Bos, SMA Bierma-Zeinstra

Submitted

Abstract

Introduction: Patients with symptomatic osteoarthritis often show fluctuating pain levels, but the cause remains largely unclear. Although bursal and tendon pathology can cause pain in patients with osteoarthritis, little is known about an association between fluctuating pain and bursal and tendon pathology. Greater trochanteric pain syndrome (GTPS) consists of a tendinitis of the insertion of the gluteus medius or minimus muscle and/or a trochanteric bursitis. This study investigates the prevalence of GTPS in patients with hip osteoarthritis and whether the co-existence of GTPS is associated with the severity of perceived pain in these patients.

Methods: In this prospective study, patients with hip osteoarthritis recruited from general practices were followed for 2 years. GTPS was diagnosed as tenderness at or around the greater trochanter, recognition of this tenderness as one of the complaints, and a painful resisted hip abduction. Pain severity was measured with the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) subscale for hip pain (0-100) and the Visual Analogue Scale (VAS) (0-100). Associations between patients' perceived hip pain and presence of GTPS were assessed using linear mixed model analysis for repeated measurements.

Results: GTPS was present in 32/205 (16%) patients at baseline and in 26/184 (14%) patients at two-year follow-up. Eight (4%) patients had GTPS at both baseline and follow-up. Presence of GTPS at one of the measurements was associated with more severe WOMAC pain (estimate 10.2, 95% CI 4.3-16.1; p=0.001) and more severe VAS pain (estimate 13.8, 95% CI 7.0-20.6; p<0.001).

Conclusion: In this cohort, one in seven patients with hip osteoarthritis had concurrent GTPS. Patients with hip osteoarthritis and GTPS at one of the measurements showed clinically significant higher pain scores at all measurements than those with hip osteoarthritis without GTPS at any of the measurements.

Introduction

Osteoarthritis (OA) of hip and knee is the most disabling type of OA and affects about 5-10% of the elderly population.[1] Until now, the development of disease-modifying OA drugs remains largely unsuccessful.[2] Therefore, mainly symptomatic treatment for OA is applied, but with only minor to moderate effectiveness.[3] Lack of treatment options to stop or reverse OA may result in joint replacement surgery.

Improvement of symptomatic therapy might be possible with better understanding of the perceived pain in OA. Patients with symptomatic OA often show fluctuating pain levels, i.e. periods with pain flares alternated with periods with much less, or even absence of, pain.[4, 5] Although this fluctuating pain pattern in OA patients is common, little is know about the mechanism behind these fluctuations.[6]

Bursal and tendon pathology are possible causes of pain in patients with OA. In radiological knee OA, patients reporting knee pain more frequently showed peri-articular lesions on magnetic resonance imaging than patients not reporting knee pain.[7]

In hip OA, few data are available on an association between the fluctuating pain patterns and bursal and tendon pathology.[4] Greater trochanter pain syndrome (GTPS) is a well-known tendinitis in the hip region with an incidence in primary care of 1.8 patients per 1000 per year.[8] Although there is continuing debate on how to define GTPS, it is generally seen as a tendinitis of the insertion of the gluteus medius or minimus muscle, or a trochanteric bursitis, or a combination of both.[9, 10] About 25% of patients with low-back pain have GTPS[11] and about 30% of patients with GTPS also have low-back pain or hip OA (defined as clinical hip OA by the American College of Rheumatology).[12]

Methods

Study design

For the present study, data were used from a randomized controlled trial that assessed the effectiveness of glucosamine sulfate on progression of OA (the GOAL trial).[13-15] In that study, eligible patients with hip OA were randomly assigned to receive either 1500 mg of oral glucosamine sulfate or placebo over a period of 2 years.

The Medical Ethics Committee of Erasmus MC approved the study design, and all patients provided written informed consent. A detailed description of the study design and outcomes are available elsewhere.[13-15] The original study showed that glucosamine sulfate was no better than placebo in reducing symptoms and progression of hip OA.

Setting and participants

The trial recruited prevalent cases of patients with hip complaints from medical records of general practices located in the south-west of the Netherlands. Patients were eligible if they met the American College of Rheumatology criteria for hip OA.[16] Patients who had undergone or were awaiting hip replacement surgery were not eligible. Also excluded from the study were patients who had a Kellgren & Lawrence (KL) score of 4 of the hip[17], renal disease, liver disease, diabetes mellitus, or a disabling co-morbid condition that would make visits to the research center impossible, as well as patients already receiving glucosamine sulfate and those unable to complete questionnaires in the Dutch language. Patients who violated the study protocol were encouraged to complete the data collection in order to limit the loss to follow-up.

Outcomes and follow-up

Using a baseline questionnaire we assessed patient characteristics, disease characteristics, and co-morbidity. Back pain severity was assessed with the question: 'In the past three months did you have osteoarthritis of your back, or pain in your back'. At baseline, radiography of the knees was performed to record the presence of radiographic OA according to the KL grading (≥ 2). Also, radiography of the hip was performed to assess radiographic severity of hip OA according to the KL grading scale (0-4).[17]

At baseline and at 2-year follow-up, patients visited the research center for a physical examination that included range of motion of the hip and painful involvement of extra-articular tissues at the hip. The greater trochanter region was assessed for tenderness at the top of the greater trochanter, as well as just above, dorsal and beneath the trochanter. In case of tenderness, patients were asked if they recognized the pain as one of their complaints.[18] In addition, we assessed whether resisted hip abduction in the extended position was painful.

GTPS was defined as the presence of tenderness at the side of the greater trochanter (on the top, or just above, dorsal or beneath) in combination with patients' recognition of this tenderness as one of the complaints, and with a painful resisted hip abduction at the ipsilateral side. Co-existence of GTPS was defined as GTPS at the site of the symptomatic hip; the symptomatic hip was designated as that with hip OA. Patients with bilateral hip symptoms were asked to indicate which hip was most affected. For patients unable to decide, the hip with the highest KL score, or the smallest internal rotation during physical examination, was used.

Severity of hip pain was measured with two validated measurement instruments: the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) subscale for hip pain and the Visual Analogue Scale (VAS). The WOMAC subscale is presented as a standardized score (0-100, where 0 indicates no symptoms and 100 indicates unbearable pain). The VAS has a 0-100 score (where 0 indicates no pain and 100 indicates unbearable pain).[19-21] If

patients had a total hip replacement during follow-up, available data were included in the analysis until surgery; data collected after surgery were assumed to be missing.

Statistical analysis

Data were analyzed using multivariate linear mixed models for repeated measurement to assess associations between patients' perceived hip pain and presence of GTPS (with a 2-year period between). This technique adjusts for the within-patient correlation for the outcomes at different measurements in each patient, and uses each outcome from each patient as a separate observation, and it therefore also allowed us to identify the between-patient variance and within-patient variance due to the presence of GTPS. The compound symmetry covariance structure was used since this yields the lowest Akaike's Information Criterium (AIC). The estimate calculated from this model is a coefficient.

Covariates used for adjustment were based on previous studies[13, 22, 23] and included: age, gender, body mass index (BMI), allocated treatment (glucosamine sulfate or placebo), and duration of hip complaints (<3 years or ≥ 3 year). We also adjusted for presence of knee OA at baseline (KL ≥ 2 in one of the knees), presence of low-back pain at baseline, and severity of radiologic hip OA at baseline (KL ≥ 2 in one of the hips). All covariates were included in the model as fixed factors. A p-value ≤ 0.05 was considered statistically significant. All analyses were conducted using SPSS version 20.0.

Results

The GOAL trial included and randomized 222 patients; of these, 111 received glucosamine sulfate and 111 received a placebo during the 2-year follow-up. The GTPS assessment was missing for 17 patients at baseline and for 18 patients at follow-up. Another 20 patients had undergone total hip replacement surgery during the follow-up period (Figure 1).

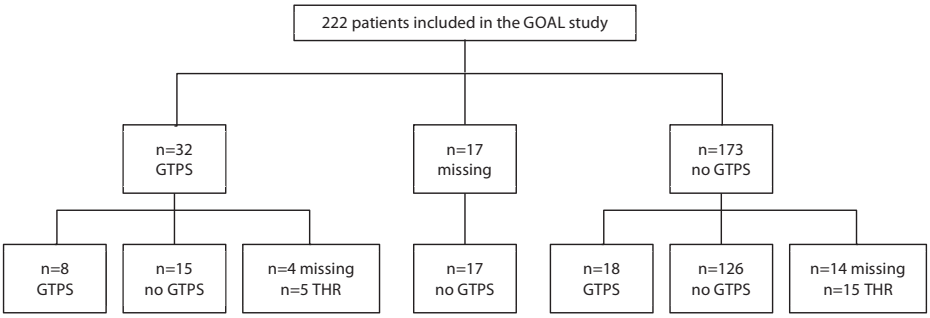


Figure 1 Flowchart of the included patients.
GTPS = greater trochanter pain syndrome, THR = Total Hip Replacement

Of the 205 patients, 32 (16%) with hip OA and GTPS assessment at baseline had symptomatic GTPS. Table 1 presents the characteristics of patients with and without GTPS at baseline. Patients with GTPS more often had a lower KL score (<2) than patients without GTPS. Radiographic knee OA was more frequently present in patients without GTPS (36%) than in patients with GTPS (19%). Low-back pain was present in about 2/3 of the patients both with and without GTPS.

Table 1 Baseline characteristics and symptom severity in patients with hip osteoarthritis with and without greater trochanteric pain syndrome.

	Hip OA with GTPS n=32	Hip OA without GTPS n=173
Female (n, %)	29 (91)	116 (67)
Age in years (mean, SD)	62.0 (8.2)	64.1 (8.5)
BMI (mean, SD)	28.5 (4.9)	27.8 (4.7)
Duration of hip complaints ≥3 years (n, %)	18 (56)	91 (53)
Radiographic severity of hip OA (n, %)		
- Kellgren&Lawrence <2	20 (62.5)	89 (51)
- Kellgren&Lawrence ≥2	12 (37.5)	84 (49)
Presence of low back pain (n, %)	23 (72)	113 (65)
Radiographic knee OA (n, %)	6 (19)	62 (36)
Radiographic hand OA (n, %)	15 (47)	95 (55)
Symptom severity		
WOMAC pain (0-100) (mean, SD)	45.9 (21.9)	32.6 (22.8)
WOMAC function (0-100) (mean, SD)	44.8 (21.2)	33.2 (22.2)
WOMAC stiffness (0-100) (mean, SD)	54.3 (23.9)	40.5 (24.1)
VAS hip pain (mean, SD)	49.0 (28.2)	29.6 (24.3)

OA = osteoarthritis; GTPS = greater trochanteric pain syndrome; BMI = body mass index; WOMAC = Western Ontario and McMasters University Osteoarthritis Index (higher score means more pain); VAS = Visual Analogue Scale (higher score means more pain), SD= standard deviation

Of the 184 patients, at follow-up 26 (14%) had GTPS. Despite a comparable prevalence of GTPS in patients with hip OA at baseline (16%) and at follow-up (14%), only 8 (4%) had GTPS at both baseline and follow-up (Figure 2).

Associations between GTPS and symptom severity

Table 2 presents the results of the multivariate linear mixed-model analysis. GTPS was significantly associated with WOMAC pain score (estimate 10.2, 95% CI 4.3-16.1; p=0.001). The estimate indicates that, when GTPS is present, the WOMAC pain score is 10.2 points higher (on a 0-100 scale). For VAS pain, GTPS was also significantly associated with an estimate of 13.8 (95% CI 7.0-20.6; p<0.001).

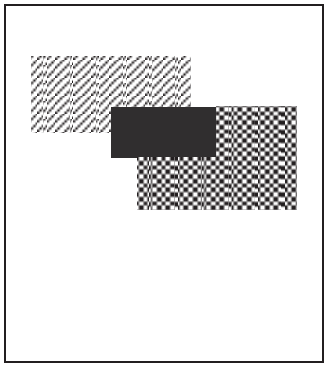


Figure 2 Distribution of the greater trochanteric pain syndrome (GTPS) at baseline and at 2-year follow-up and overlap between them.
Total n=167
Striped area GTPS at baseline (n=15); Dotted area GTPS at 2-year follow-up (n=18); Black area GTPS at baseline and at 2-year follow-up (n=8); Excluded were persons with total hip replacement during follow-up, or missing the GTPS examination at baseline or at 2-year follow-up.

Table 3 presents the explained variances of the covariates included in the linear mixed model. GTPS explains 7% of the between-patient variance for WOMAC pain; however, GTPS explains <1% of the within-patient variance for WOMAC pain. The total model explains 36% of the between-patient variance for WOMAC pain; with 7% (20% of the models explained between-patient variance) GTPS is an important factor in this model.

In the model for VAS pain, GTPS explains 16% of the between-patient variance and 2.7% of the within-patient variance. The total model explains 39% of the between-patient variance for VAS pain; with 16% (41% of the models explained between-patient variance) GTPS is also an important factor in this model. The small within-patient variance in both models indicates that patients with hip OA that have or had GTPS at one of the measurements have more pain than patients with hip OA that did not have GTPS at one of two measurements.

Table 2 Results of multivariable linear mixed model analysis for GTPS and perceived severity of pain at baseline and 2-year follow-up (n=220).

	WOMAC pain			VAS hip pain		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
GTPS (at baseline and at 2-year FU)	10.2	4.3 – 16.1	0.001	13.8	7.0 – 20.6	<0.001
Knee OA at baseline (KL≥2)	1.3	-4.3 – 6.9	0.65	0.3	-5.9 – 6.5	0.92
Back pain at baseline	13.7	8.4 – 19.0	<0.001	11.9	6.1 – 17.7	<0.001
Hip OA at baseline (KL≥2)	6.7	1.6 – 11.8	0.010	9.2	3.6 – 14.8	0.001

Analysis adjusted for baseline variables gender, age (years), body mass index (kg/m^2), allocated treatment (glucosamine sulfate or placebo), and duration of complaints (<3 years or ≥3 years). FU = follow-up; WOMAC = Western Ontario and Mc Masters University Osteoarthritis Index; VAS = Visual Analogue Scale; OA = osteoarthritis; KL = Kellgren & Lawrence grading of radiologic OA; GTPS = greater trochanter pain syndrome

Table 3 Between-patient and within-patient variances for GTPS and pain at baseline and at 2-year follow-up (n=220).

	WOMAC pain		VAS hip pain	
	bP (% explained)	wP (% explained)	bP (% explained)	wP (% explained)
IC only	263	281	268	413
IC + adjustments*	220 (16%)		225 (16%)	
IC + knee OA at baseline (KL≥2)	259 (2%)		266 (1%)	
IC + back pain at baseline	207 (21%)		221 (16%)	
IC + hip OA at baseline (KL≥2)	262 (0%)		260 (3%)	
IC + GTPS (at baseline and FU)	245 (7%)	280 (<1%)	226 (16%)	424 (2,7%)
Total model**	168 (36%)		164 (39%)	

FU = follow-up; WOMAC = Western Ontario and McMaster Universities, VAS = Visual Analogue Scale, bP = between-patient variance, wP = within-patient variance, IC = intercept, OA = osteoarthritis, GTPS = greater trochanter pain syndrome * Adjusted for for baseline variables gender, age (years), body mass index (kg/m^2), allocated treatment (glucosamine sulfate or placebo), duration of complaints (<3 years or ≥3 years). ** In the total model all variables and adjustments are included: GTPS, gender, age (years), body mass index (kg/m^2), allocated treatment (glucosamine sulfate or placebo), duration of complaints (<3 years or ≥3 years), knee OA, back pain and severity of radiologic OA.

Discussion

In this primary care cohort, one in seven patients with hip OA had concurrent GTPS. Patients with hip OA and GTPS showed clinically significant higher pain scores than patients with hip OA without GTPS.[24]

To our knowledge this is the first study to report the incidence and analysis of GTPS in hip OA patients. In a population aged 50-79 years with knee OA or at risk for knee OA, Segal et al. found a prevalence of GTPS of 17.6% (based on tenderness at physical examination) and found that GTPS was related to the presence of ipsilateral knee OA.[25] In the present longitudinal study with measurements at baseline and 2-year follow-up, data were analyzed using linear mixed model analysis. An earlier study, included in a PhD thesis[26] assessed in the same data whether the co-existence of GTPS was associated with more pain, using a linear regression model with backward selection. However, we believe that use of a linear mixed model with repeated measurements is more appropriate since this technique adjusts for the within-patient correlation for the symptom severity scores at different measurement points, and also clearly shows both the within-patient variance and between-patient variance due to GTPS.

Based on these analyses, it showed that more between-patient variance was explained by GTPS than within-patient variance. This implies that patients with hip OA who had GTPS at one of the measurements have more pain even when GTPS is absent than patients who did not have GTPS at one of the occasions. It also implies that patients with GTPS may have factors in common that correlate with reported pain ranging from biomechanical factors like

a disturbed walking pattern to the presence of sensitized pain pattern. However, because of the omission of such factors in our study we were not able to study any causal mechanism behind the association between GTPS and increased pain.

About two thirds of our hip OA patients reported low-back pain. The presence of low-back pain aggravated the severity of symptoms in hip OA even more than the presence of GTPS. Musculoskeletal co-morbidity is known to influence the severity of symptoms in OA.[27, 28] Co-existent low-back pain is also known to predict future pain in those with clinical hip OA.[29] The presence of co-existent low-back or buttock pain, often in combination with spine OA, may also be a cause of persisting pain at that location after total hip replacement and may lead to dissatisfaction with the surgery.[30]

At present, no data are available on the influence of co-existent GTPS on the outcome of any treatment for hip OA. On the other hand, the influence of co-existent hip OA or low-back pain was studied in a trial using local corticosteroid injection in patients with GTPS.[12, 31] There was a significant short-term effect of local corticosteroid injection in the total group, but also to a similar or even greater degree in the subgroup of patients with co-existent low-back pain or hip OA.[12] This implies that the subgroup of patients with co-morbidity benefits as much from injection therapy as the total group.

A limitation of the present study is the lack of consensus on the diagnostic criteria for GTPS. Related to this, few data are available on the validity or reliability of diagnostic criteria for this condition (although we did not evaluate these properties in the present study). Although some studies mentioned trochanteric tenderness and recognition of the pain as diagnostic criteria[18, 32-34], others report on additional diagnostic tests such as a positive Trendelenburg sign, painful resisted abduction, painful resisted internal rotation, and a painful FABER test (flexion, abduction, external rotation).[10, 35, 36] The present study used trochanteric tenderness, patients' recognition of the pain, and resisted painful abduction, as diagnostic criteria. When analyzing our data using a less stringent diagnosis of GTPS (trochanteric tenderness and recognition of the pain only) the prevalence of GTPS was higher but the association with perceived pain in hip OA remained about the same.

In our study patients were selected from databases of general practitioners (GPs) who diagnosed patients with hip OA. Because these patients were contacted by their GP, this study used prevalent cases of hip OA in general practice. Therefore, these results should be interpreted with caution and cannot be directly extrapolated to patients with hip OA visiting their GP for pain and patients with hip OA visiting secondary caregivers.

In clinical practice it is important to identify in patients with hip OA, the concurrent GTPS or other musculoskeletal co-morbidity since these patients often show more pain. Treatment should be aimed at both the musculoskeletal co-morbidity and the hip OA, but also, when known at the causal mechanisms behind it. It has been shown that patient with GTPS demonstrate significant weakness of the hip abductor muscles, even bilaterally, compared to healthy individuals.[37] It is not clear whether GTPS precedes hip abductor weakness or vice

versa, however this could be a future point-of-action for therapy. An ongoing trial is, at this moment, studying treatment of GTPS comparing wait-and-see to corticosteroid injection to physiotherapy.[38] New research should also assess whether pain sensitization mechanisms are present in case of musculoskeletal co-morbidity, and search for subsequent adequate treatment.

Conclusions

In this cohort study, one in seven patients with hip osteoarthritis had concurrent GTPS. Patients with hip OA and GTPS at one of the measurements showed clinically significant higher pain scores than patients with hip OA without GTPS at any of the measurements.

References

1. Odding E, Valkenburg HA, Algra D, Vandenouweland FA, Grobbee DE, Hofman A. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study. Ann Rheum Dis 1998; 57: 203-208.
2. Felson DT, Kim YJ. The futility of current approaches to chondroprotection. Arthritis Rheum 2007; 56: 1378-1383.
3. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007; 15: 981-1000.
4. Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis 2012; 71: 1517-1523.
5. Leffondre K, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. J Clin Epidemiol 2004; 57: 1049-1062.
6. Moskowitz RW, Sunshine A, Hooper M, Olson NZ, Cawkwell GD. An analgesic model for assessment of acute pain response in osteoarthritis of the knee. Osteoarthritis Cartilage 2006; 14: 1111-1118.
7. Hill CL, Gale DR, Chaisson CE, Skinner K, Kazis L, Gale ME, et al. Periarticular lesions detected on magnetic resonance imaging: prevalence in knees with and without symptoms. Arthritis Rheum 2003; 48: 2836-2844.
8. Lievense A, Bierma-Zeinstra S, Schouten B, Bohnen A, Verhaar J, Koes B. Prognosis of trochanteric pain in primary care. Br J Gen Pract 2005; 55: 199-204.
9. Karpinski MR, Piggott H. Greater trochanteric pain syndrome. A report of 15 cases. J Bone Joint Surg Br 1985; 67: 762-763.
10. Fearon AM, Scarvell JM, Cook JL, Neeman T, Cormick W, Smith PN. Greater trochanteric pain syndrome: defining the syndrome. Br J Sports Med 2013; 47: e2.
11. Collee G, Dijkmans BA, Vandenbroucke JP, Cats A. Greater trochanteric pain syndrome (trochanteric bursitis) in low back pain. Scand J Rheumatol 1991; 20: 262-266.
12. Brinks A, van Rijn RM, Willemsen SP, Bohnen AM, Verhaar JA, Koes BW, et al. Corticosteroid injections for greater trochanteric pain syndrome: a randomized controlled trial in primary care. Ann Fam Med 2011; 9: 226-234.
13. Rozendaal RM, Koes BW, van Osch GJ, Uitterlinden EJ, Garling EH, Willemsen SP, et al. Effect of glucosamine sulfate on hip osteoarthritis: a randomized trial. Ann Intern Med 2008; 148: 268-277.
14. Rozendaal RM, Koes BW, Weinans H, Uitterlinden EJ, van Osch GJ, Ginai AZ, et al. The effect of glucosamine sulphate on osteoarthritis: design of a long-term randomised clinical trial [ISRCTN54513166]. BMC Musculoskelet Disord 2005; 6: 20.
15. Rozendaal RM, Uitterlinden EJ, van Osch GJ, Garling EH, Willemsen SP, Ginai AZ, et al. Effect of glucosamine sulphate on joint space narrowing, pain and function in patients with hip osteoarthritis; subgroup analyses of a randomized controlled trial. Osteoarthritis Cartilage 2009; 17: 427-432.
16. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.

17. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494-502.
18. Anderson TP. Trochanteric bursitis: diagnostic criteria and clinical significance. Arch Phys Med Rehabil 1958; 39: 617-622.
19. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-1840.
20. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW, et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 2004; 63: 36-42.
21. Jensen MP, Miller L, Fisher LD. Assessment of pain during medical procedures: a comparison of three scales. Clin J Pain 1998; 14: 343-349.
22. van Dijk GM, Dekker J, Veenhof C, van den Ende CH. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. Arthritis Rheum 2006; 55: 779-785.
23. Peters TJ, Sanders C, Dieppe P, Donovan J. Factors associated with change in pain and disability over time: a community-based prospective observational study of hip and knee osteoarthritis. Br J Gen Pract 2005; 55: 205-211.
24. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Medical care 2003; 41: 582-592.
25. Segal NA, Felson DT, Torner JC, Zhu Y, Curtis JR, Niu J, et al. Greater trochanteric pain syndrome: epidemiology and associated factors. Arch Phys Med Rehabil 2007; 88: 988-992.
26. Brinks A. Greater trochanteric pain syndrome in general practice. General Practice, vol. PhD. Rotterdam: Erasmus University Rotterdam 2011:143.
27. Reeuwijk KG, de Rooij M, van Dijk GM, Veenhof C, Steultjens MP, Dekker J. Osteoarthritis of the hip or knee: which coexisting disorders are disabling? Clin Rheumatol 2010; 29: 739-747.
28. Suri P, Morgenroth DC, Kwoh CK, Bean JF, Kalichman L, Hunter DJ. Low back pain and other musculoskeletal pain comorbidities in individuals with symptomatic osteoarthritis of the knee: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2010; 62: 1715-1723.
29. Stupar M, Cote P, French MR, Hawker GA. The association between low back pain and osteoarthritis of the hip and knee: a population-based cohort study. J Manipulative Physiol Ther 2010; 33: 349-354.
30. Parvizi J, Pour AE, Hillibrand A, Goldberg G, Sharkey PF, Rothman RH. Back pain and total hip arthroplasty: a prospective natural history study. Clin Orthop Relat Res 2010; 468: 1325-1330.
31. Brinks A, van Rijn RM, Bohnen AM, Slee GL, Verhaar JA, Koes BW, et al. Effect of corticosteroid injection for trochanter pain syndrome: design of a randomised clinical trial in general practice. BMC Musculoskelet Disord 2007; 8: 95.
32. Little H. Trochanteric bursitis: a common cause of pelvic girdle pain. Can Med Assoc J 1979; 120: 456-458.
33. Shbeeb MI, Matteson EL. Trochanteric bursitis (greater trochanter pain syndrome). Mayo Clin Proc 1996; 71: 565-569.
34. Schapira D, Nahir M, Scharf Y. Trochanteric bursitis: a common clinical problem. Arch Phys Med Rehabil 1986; 67: 815-817.

35. Bird PA, Oakley SP, Shnier R, Kirkham BW. Prospective evaluation of magnetic resonance imaging and physical examination findings in patients with greater trochanteric pain syndrome. Arthritis Rheum 2001; 44: 2138-2145.
36. Lequesne M, Mathieu P, Vuillemin-Bodaghi V, Bard H, Djian P. Gluteal tendinopathy in refractory greater trochanter pain syndrome: diagnostic value of two clinical tests. Arthritis Rheum 2008; 59: 241-246.
37. Allison K, Vicenzino B, Wrigley TV, Grimaldi A, Hodges PW, Bennell KL. Hip Abductor Muscle Weakness in Individuals with Gluteal Tendinopathy. Med Sci Sports Exerc 2016; 48: 346-352.
38. Mellor R, Grimaldi A, Wajswelner H, Hodges P, Abbott JH, Bennell K, et al. Exercise and load modification versus corticosteroid injection versus 'wait and see' for persistent gluteus medius/minimus tendinopathy (the LEAP trial): a protocol for a randomised clinical trial. BMC Musculoskelet Disord 2016; 17: 196.

CHAPTER 8

General discussion

The aim of the work presented in this thesis was to assess the effectiveness of intramuscular corticosteroid injection in patients with painful hip osteoarthritis (OA), to gain insight into diagnosing hip OA, and into the course of pain and comorbidities influencing complaints in patients with hip OA.

First, we conducted a randomized controlled trial (RCT) that assessed the effectiveness of an intramuscular corticosteroid injection compared to an intramuscular placebo injection in patients with painful hip OA. In a systematic review we then studied the value of anesthetic hip joint injection in diagnosing hip OA. We also examined associations between clinical symptoms in patients with hip OA and biomarkers. A systematic review was made of the available literature and associations were assessed between patients' symptoms due to hip OA and weather conditions. Finally, we focused on the influence of the greater trochanter pain syndrome (GTPS) on hip pain severity in patients with hip OA.

This chapter presents the main findings of our work in relation to existing evidence and addresses some methodological challenges. The chapter closes by presenting some implications for daily practice and ideas for future research.

Non-operative treatment of hip OA

Several international guidelines are available for non-operative treatment of hip OA and many of the recommendations are generally agreed upon.[1-4] The current Dutch guideline for the diagnosis and treatment hip OA has a multidisciplinary design and is supported by both primary care providers and secondary care providers.[3] This guideline (dating from 2007) is under currently revision; an updated guideline is expected in due course.

Treatment of symptomatic OA begins with non-pharmacological management including education, exercise, weight loss, and assistive devices.[4] These therapies can be combined with pain medication. Acetaminophen is still the first-line treatment, followed by non-steroidal anti-inflammatory agents (NSAIDs) and opiates (tramadol). Another possibility is an intra-articular corticosteroid injection; most international guidelines recommend this treatment option for knee OA and hip OA.[1-4] However, because the hip joint cannot be palpated and is adjacent to important neurovascular structures, hip joint injection is best performed under fluoroscopic or ultrasound guidance. In clinical practice this often results in delay or refraining from this type of treatment, because an appointment at the radiology department has to be planned. In contrast, an intramuscular corticosteroid injection can be given immediately.

In Chapter 3 we show that an intramuscular corticosteroid injection has a systemic effect on hip pain reduction in patients with hip OA during a 12-week follow-up period. This non-operative alternative treatment might lengthen the non-operative management of patients with hip OA in primary care, or postpone surgical treatment in secondary care.

It was interesting that the effect of the intramuscular corticosteroid injection was maintained during the entire 12-week follow-up period. The mid-term (±3 months) effect of intra-articular corticosteroid compared to placebo has been demonstrated in a meta-analysis using individual patient data from patients with hip OA, from two hip OA trials with medium to low risk of bias. At mid-term follow-up (3 months) the pooled mean difference (MD) for intra-articular injection was 13.6 (95% CI 3.5 to 23.6) (scale 0-100); this result was similar to the effect of intramuscular injection in our trial, i.e. MD -1.2 (95% CI -2.3 to -0.2) (scale 0-10).[5] On the other hand, a recent systematic review (including 5 studies) did not find this mid-term effect of intra-articular corticosteroids in patients with hip OA.[6] Moreover, a recent Cochrane review (including 27 trials with 1767 participants) on knee OA and intra-articular corticosteroid injection, also found no mid-term effect on pain reduction.[7]

In clinical practice, repeated intra-articular corticosteroid injection is under debate because of the assumed risk of progression of OA due to chondrotoxicity. In basic science literature intra-articular corticosteroid treatment has been associated with toxicity to chondrocytes.[8]

A recent systematic review on the effect of intra-articular corticosteroids on articular cartilage identified only one clinical trial in humans. All other studies were *in vitro* human chondrocyte studies or *in vivo* animal studies.[8] The one human clinical trial studied the effect of 40 mg triamcinolone acetate injection in patients with knee OA by administering injections every 3 months for a 2-year period; the results show no difference in radiographic narrowing in the corticosteroid group or the placebo group, suggesting that multiple intra-articular corticosteroid injections can safely be given with regard to structural progression.[9]

Another important point is the assumed increased risk of prosthesis infection after intra-articular injection with corticosteroids. An intra-articular hip injection in the year preceding hip replacement increases the risk of prosthesis infection (3.3% versus 2.4% for patients who did not receive intra-articular injection) in a retrospective cohort study.[10] This increased risk of prosthesis injection has also been shown in a retrospective cohort study for systemic corticosteroid treatment for more than 1 week (OR 2.19 corticosteroid treatment versus no corticosteroid treatment).[11] For a single intramuscular injection no literature is available on the assessed risk of prosthesis infection. A recent systematic review on this subject included 9 nine studies with important methodological flaws.[12] 8 of the 9 studies were retrospective and confounding factors were poorly addressed. This systematic review concludes that there is insufficient evidence to conclude that intra-articular corticosteroid injection increases the risk of prosthesis infection.

According to a predefined subgroup analysis, the effects of hip pain reduction in the corticosteroid group were larger for patients from secondary care than for patients from primary care: Numerical Rating Scale (NRS) in rest at 2-week follow-up: between-group difference -2.3 (95% CI -4.4 to -0.2); between-group difference in primary care -0.9 (95% CI -2.0 to 0.2). These effects were present despite the relatively small group of patients from secondary care (n=26) compared to the group recruited from primary care (n=80). This suggests that, even

after referral to secondary care, non-operative treatment can be effective in pain reduction and that total hip replacement (THR) should not be offered immediately.

A challenge we experienced was recruiting patients to participate in our placebo-controlled trial. Although we assessed 422 patients with hip OA for eligibility, we were unable to include our pre-calculated sample size of 128 patients. Of the 422 assessed patients, 92 (22%) declined to participate, mostly because they did not want to risk receiving a placebo. Of the 334 patients that did not immediately refuse, 30% (n=101) did not use any pain medication despite moderate to severe pain (NRS ≥3; scale 0-10). In clinical practice, patients consider the effect of pain medications such as acetaminophen and NSAIDs to be too small. In a cohort of patients with knee OA, 74% of patients used over-the-counter pain medication; however, only 47% rated this treatment as very effective.[13] Patients with severe knee OA used less over-the-counter pain medication (67%) compared to those with mild and moderate knee OA, i.e. 72.9% and 77.2%, respectively.[13] Because clinical practice shows that not all patients with OA with moderate to severe pain take pain medication, future clinical research should set less stringent inclusion criteria on this item.

Diagnosis in hip pain

Hip pain can arise from different sources, both intra-articular and extra-articular. It is important to correctly classify the disease that is the source of hip pain, especially when treatment includes surgery (such as THR). Careful history taking and physical examination can often differentiate between hip OA and other sources of symptoms.[14] However, in some cases presentation is nonspecific and the diagnosis remains challenging. Although the presence of limping, groin pain, and limited internal rotation of the hip are more predictive for hip disorders, these symptoms are also seen in patients with spine disease, or both hip disease and spine disease.[15] Additional radiographic examination will not always be helpful to diagnose hip OA. For example, in two large epidemiological studies, Kim et al. showed that many people with painful hips do not have radiographic evidence of hip OA and many patients with radiographic OA do not have hip pain.[16] Moreover, hip pain is also associated with disc space narrowing at level L1-2 (men OR = 2.0, and women OR = 1.7) and at L2-3 (women OR = 1.6).[17]

To differentiate between hip pain originating from the hip joint and other pathology (e.g. spinal disease), an anesthetic hip joint injection is used in orthopaedic practice. However, in our systematic review (Chapter 4) we conclude that, based on the available evidence, no recommendation can be made regarding the use of hip injection for diagnosing hip OA because of the high risk of bias of the included studies. The available evidence consisted of 9 studies (with a total of 556 patients) with medium to high risk of bias. Although all studies used THR as reference standard, there was considerable verification bias. In our pooled results, 75% of

the patients that had reduction in pain after injection received a THR, whereas in patients that did not have pain reduction after injection only 15% received a THR.

To check the data we found in the published studies from abroad, we performed an explorative retrospective cohort study in patients that received a diagnostic hip injection between January 2009 and December 2010 in two Dutch hospitals (Erasmus Medical Centre Rotterdam and Elisabeth Hospital Tilburg). We identified 103 patients that had a diagnostic hip injection. However, in this retrospective setting, pain scores after diagnostic injection were missing for most patients. Moreover, although a final diagnosis was made in 99 patients, for 30 of these patients we could not retrieve their level of satisfaction or pain relief after final treatment. These data are in accordance with other retrospective studies on the diagnostic value of anesthetic hip joint injection and did not result in new insights.[18-23] However, based on lacking data in such retrospective studies, we emphasize the importance of routine collecting of standardized patient-reported outcome measures in clinical practice.

So far, the value of intra-articular diagnostic hip injection remains under debate. Based on the available evidence we cannot recommend its use in clinical practice.

Course of pain in hip OA

Patients diagnosed with hip OA often ask their healthcare providers about the prognosis of their complaints, i.e. they would like to know about the progression of OA and related complaints. For healthcare providers this is a difficult question because the available knowledge and data are mainly on the group level. It is reported, on group level, that pain and functional status deteriorate slowly over time for hip OA.[24] Beside this slow progression, symptoms can also vary greatly on a time (e.g. days/weeks) basis. These flairs in pain are associated with disability, poorer sleep quality, productivity losses, reduced quality of life, and higher healthcare resource use.[25] It also is known that some patients are fast progressors and some slow progressors; however, this is difficult to predict for the individual patient. If physicians are able to identify patients at high risk of fast progression of OA, we could tailor our advice to the individual patient and adjust treatment accordingly. Prognostic factors to predict the course of hip pain due to OA are limited.[26] To identify possible trajectories of pain in hip OA over time, latent class growth analysis (LCGA) can be used. This statistical technique attempts to group people who are similar in their response to measured variables or growth trajectories. This method allows to discriminate between progressive trajectory disease and non-progressive disease,[27, 28] and is applied to repeated measurement data. Previously, these trajectories were difficult to identify due to the lack of repeated measurements. For example, when only one follow-up moment was used, the patient could be defined as a progressor or non-progressor depending on their temporary flair or non-flair period, whereas their overall symptomatic progression over several time points might show a different pattern.

LCGA has been used in patients with hip OA with 3-monthly measurements of pain during a 2-year follow-up study. LCGA was able to discriminate five distinct trajectories of pain: i.e. mild pain, moderate pain, always (severe) pain, regularly progressive pain, and highly progressive pain.[28] In another cohort of patients with early symptomatic hip OA and a 5-year follow-up, four different pain trajectories were found using LCGA: mild pain, moderate decrease, moderate progression, and severe pain. Factors associated with more severe pain trajectories were lower education, higher activity limitation scores, frequent use of pain reinterpretation as coping strategy, and painful internal hip rotation.[29]

In the future, when a risk assessment score for individual patients can be made and validated for the trajectory of progression in hip pain, patients can be educated and treated according to their individual risk.

Biomarkers are defined as characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[30] However, OA-specific biomarkers are not joint specific when assessed in serum or urine. If such biomarkers could predict progression of hip pain or hip OA in individual patients, this would be of substantial clinical value. However, until now, again few publications are available on biomarkers and the prediction of OA progression.[31] Most studies present association data on group level, and no discriminative areas under the curve or predictive values.

In Chapter 5 we assessed the association between cartilage biomarkers (uCTXII and uCIIM) and clinical symptoms in patients with hip OA using the previously defined pain trajectories based on LCGA. Both these markers are derivatives of type II collagen and degraded by enzymes during cartilage erosion and excreted in urine. CTXII has been studied extensively in knee as well as hip OA.[31] Our study showed that in patients with mild to moderate hip OA, uCTX-II and uCIIM were not cross-sectionally associated with hip pain at 6-monthly intervals during the 2-year follow-up. However, patients in the moderate pain trajectory and in the highly progressive pain trajectory were more likely to have a higher loguCTX-II at baseline than patients in the mild pain trajectory.

A recent prediction model for knee OA shows that 'questionnaire-based' risk factors, age/gender/BMI, a genetic risk score, or uCTX-II levels alone are not good predictors of incident radiographic knee OA.[32] Also, a combination of these risk factors has a relatively low predictive value for knee OA. However, a model that includes doubtful minor radiographic degeneration reached good predictive value and is applicable in clinical practice. A recent systematic review on the use of biomarkers for risk assessment shows that limited data are available on hip OA.[31] If, in the future, biomarkers, together with other variables, could be included in a risk assessment score for individual patients for hip OA, then biomarkers could be used in clinical practice. However, at the moment, biomarkers show no or only small associations and offer no additional value over variables that are easily assessed, e.g. reported morning stiffness, painful internal rotation, etc.

As mentioned previously, patients with OA show daily or weekly fluctuations in pain symptoms.[25, 28] Because patients often report that weather conditions influence their symptoms, this could be a contributing factor.[33] In Chapter 6 it is shown that in patients with hip OA, barometric pressure and relative humidity influence OA pain and disability. However, the contribution of these weather variables to the severity of OA symptoms is not considered to be clinically relevant.

The effect of weather variables has also been studied in low back pain; in this case, the speed of wind and wind gusts showed an association with back pain; however, the magnitude of the increase was, again, not considered to be clinically relevant.[34]

Previous studies on hip OA and weather show no consistent correlation with patients' pain. This inconsistency might be caused by differences in the methods of data collection and statistical analyses. Based on our findings, as well as the inconsistency of previous studies on hip OA and weather and the findings related to low back pain, we suggest that no new studies should focus on musculoskeletal disorders and weather variables. In clinical practice, patients can be informed that the weather has practically no influence on symptoms related to hip OA.

Hip OA and comorbidities

The onset of musculoskeletal comorbidity, e.g. low back pain or tendinopathy, can cause an increase in pain in patients with hip OA. Parvizi et al. reported that in patients with hip OA and pre-operative low back pain, this back pain does not resolve after THR in one third of patients; [35] this might lead to dissatisfaction after THR.

Another comorbidity is greater trochanter pain syndrome (GTPS), which is a trochanteric bursitis and/or a tendinitis of the insertion of the gluteus medius or gluteus minimus muscle. In Chapter 7 we concluded that one in seven patients with hip OA had concomitant GTPS. Moreover, patients with concomitant GTPS reported significantly higher scores for hip pain than patients with hip OA alone.

In patients with hip OA, it is important to identify concurrent GTPS or other musculoskeletal co-morbidity, since these patients often report more pain. The treatment of patients with hip OA and GTPS should be aimed at both conditions. GTPS can be treated by wait-and-see, physiotherapy (hip abductor weakness), analgesics, and a local corticosteroid injection. Even, in patients with GTPS and comorbidities, such as low back pain and/or hip OA, the effect of a corticosteroid injection in the trochanteric bursa is greater (58% recovered) compared to patients with GTPS alone (32% recovered).[36]

Implications for clinical practice and future research

This thesis shows that although diagnostic anesthetic hip injection is frequently used, evidence for the diagnostic value of this test is limited and there is a lack of studies, which have a low risk of bias. Therefore, future research should preferably consist of an observational prospective cohort of patients with hip pain atypical for hip OA, or patients with hip OA and concomitant lumbar spine OA visiting the orthopaedic outpatient clinic. In this cohort, severity of pain and patients' satisfaction should be measured using validated questionnaires at pre-injection, post-injection, and after subsequent treatment, e.g. THR.

Such studies should help establish: i) the diagnostic value of intra-articular anesthetic hip injection in patients with atypical hip pain who consult an orthopaedic surgeon; ii) the effect of intra-articular anesthetic hip injection on atypical hip pain; iii) the type/effect of therapies given to these patients; iv) outcomes after the selected therapies; v) and clinical differences between patients with atypical hip pain and a final treatment for hip OA (THR) compared with patients with atypical hip pain and a different type of final treatment.

This thesis also shows that, based on the results of our blinded RCT evaluating the effectiveness of an intramuscular corticosteroid injection versus an intramuscular placebo injection, there is a pain-reducing effect in patients with painful hip OA for at least 12 weeks.

This information could change the treatment strategy for hip OA, because this means an additional treatment option is available for patients with painful hip OA. Since this intramuscular injection can be given in both primary and secondary care, general practitioners will be able to treat patients with hip OA for a longer period of time in primary care. However, since this is the first trial assessing the effect of intramuscular corticosteroid injection for painful hip OA, our findings need to be confirmed in additional trials. Moreover, cost-effectiveness compared to usual care and compared to intra-articular injection is lacking. Our results need to be validated in a study with a longer follow-up period, assessing multiple injections and including patients from both primary and secondary care.

Finally, our study did not assess the effect of intramuscular corticosteroid injection compared to intra-articular injection. If future research shows at least a similar effect of intramuscular and intra-articular injection, or shows effective mid-term or even long-term effects, then intramuscular injection could replace intra-articular injection. However, this should (preferably) be investigated in a blinded randomized controlled inferiority trial comparing the two types of corticosteroid injection. The aim of all these studies is to further improve the diagnosis and treatment of patients with painful hip osteoarthritis.

References

1. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. Osteoarthritis Cartilage 2007; 15: 981-1000.
2. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, 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 2010; 18: 476-499.
3. Dutch Orthopaedic Association. Guideline diagnostics and treatment of hip osteoarthritis and knee osteoarthritis. Nijmegen 2007.
4. Nelson AE, Allen KD, Golightly YM, Goode AP, Jordan JM. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. bone and joint initiative. Semin Arthritis Rheum 2014; 43: 701-712.
5. van Middelkoop M, Arden NK, Atchia I, Birrell F, Chao J, Rezende MU, et al. The OA Trial Bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. Osteoarthritis Cartilage 2016.
6. McCabe PS, Maricar N, Parkes MJ, Felson DT, O'Neill TW. The efficacy of intra-articular steroids in hip osteoarthritis: A systematic review. Osteoarthritis Cartilage 2016.
7. Juni P, Hari R, Rutjes AW, Fischer R, Silletta MG, Reichenbach S, et al. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database Syst Rev 2015; 10: CD005328.
8. Wernecke C, Braun HJ, Dragoo JL. The Effect of Intra-articular Corticosteroids on Articular Cartilage: A Systematic Review. Orthop J Sports Med 2015; 3.
9. Raynauld JP, Buckland-Wright C, Ward R, Choquette D, Haraoui B, Martel-Pelletier J, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2003; 48: 370-377.
10. Ravi B, Escott BG, Wasserstein D, Croxford R, Hollands S, Paterson JM, et al. Intraarticular hip injection and early revision surgery following total hip arthroplasty: a retrospective cohort study. Arthritis Rheumatol 2015; 67: 162-168.
11. Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. J Hosp Infect 2015; 89: 82-89.
12. Pereira LC, Kerr J, Jolles BM. Intra-articular steroid injection for osteoarthritis of the hip prior to total hip arthroplasty : is it safe? a systematic review. The bone & joint journal 2016; 98-B: 1027-1035.
13. Posnett J, Dixit S, Oppenheimer B, Kili S, Mehin N. Patient preference and willingness to pay for knee osteoarthritis treatments. Patient preference and adherence 2015; 9: 733-744.
14. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991; 34: 505-514.
15. Brown MD, Gomez-Marin O, Brookfield KF, Li PS. Differential diagnosis of hip disease versus spine disease. Clin Orthop Relat Res 2004: 280-284.
16. Kim C, Nevitt MC, Niu J, Clancy MM, Lane NE, Link TM, et al. Association of hip pain with radiographic evidence of hip osteoarthritis: diagnostic test study. BMJ 2015; 351: h5983.

17. de Schepper EI, Damen J, Bos PK, Hofman A, Koes BW, Bierma-Zeinstra SM. Disk degeneration of the upper lumbar disks is associated with hip pain. Eur Spine J 2013; 22: 721-726.
18. Faraj AA, Kumaraguru P, Kosygan K. Intra-articular bupivacaine hip injection in differentiation of coxarthrosis from referred thigh pain: a 10 year study. Acta Orthop Belg 2003; 69: 518-521.
19. Illgen RL, 2nd, Honkamp NJ, Weisman MH, Hagenauer ME, Heiner JP, Anderson PA. The diagnostic and predictive value of hip anesthetic arthrograms in selected patients before total hip arthroplasty. J Arthroplasty 2006; 21: 724-730.
20. Odoom JE, Allen GM, Wilson DJ. Response to local anaesthetic injection as a predictor of successful hip surgery. Clin Radiol 1999; 54: 430-433.
21. Pateder DB, Hungerford MW. Use of fluoroscopically guided intra-articular hip injection in differentiating the pain source in concomitant hip and lumbar spine arthritis. Am J Orthop 2007; 36: 591-593.
22. Poiraudeau S, Martinez M, Anract P, Chevrot A, Revel M. Value of hip anesthesia to characterize the main origin of pain in hip-spine osteoarthritis. Europa Medicophysica 2000; 36: 61-66.
23. Yoong P, Guirguis R, Darrah R, Wijeratna M, Porteous MJ. Evaluation of ultrasound-guided diagnostic local anaesthetic hip joint injection for osteoarthritis. Skeletal Radiol 2012; 41: 981-985.
24. van Dijk GM, Dekker J, Veenhof C, van den Ende CH. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. Arthritis Rheum 2006; 55: 779-785.
25. Hutchings A, Calloway M, Choy E, Hooper M, Hunter DJ, Jordan JM, et al. The Longitudinal Examination of Arthritis Pain (LEAP) study: relationships between weekly fluctuations in patient-rated joint pain and other health outcomes. J Rheumatol 2007; 34: 2291-2300.
26. Lievense AM, Koes BW, Verhaar JA, Bohnen AM, Bierma-Zeinstra SM. Prognosis of hip pain in general practice: a prospective followup study. Arthritis Rheum 2007; 57: 1368-1374.
27. Leffondre K, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. J Clin Epidemiol 2004; 57: 1049-1062.
28. Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA, et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. Ann Rheum Dis 2012; 71: 1517-1523.
29. Bastick AN, Verkleij SP, Damen J, Wesseling J, Hilberdink WK, Bindels PJ, et al. Defining hip pain trajectories in early symptomatic hip osteoarthritis - 5 year results from a nationwide prospective cohort study (CHECK). Osteoarthritis Cartilage 2016; 24: 768-775.
30. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharm & Ther 2001; 69.
31. Hosnijeh FS, Runhaar J, van Meurs JB, Bierma-Zeinstra SM. Biomarkers for osteoarthritis: Can they be used for risk assessment? A systematic review. Maturitas 2015; 82: 36-49.
32. Kerkhof HJ, Bierma-Zeinstra SM, Arden NK, Metrustry S, Castano-Betancourt M, Hart DJ, et al. Prediction model for knee osteoarthritis incidence, including clinical, genetic and biochemical risk factors. Annals of the rheumatic diseases 2014; 73: 2116-2121.
33. Laborde JM, Dando WA, Powers MJ. Influence of weather on osteoarthritics. Soc Sci Med 1986; 23: 549-554.
34. Steffens D, Maher CG, Li Q, Ferreira ML, Pereira LS, Koes BW, et al. Effect of weather on back pain: results from a case-crossover study. Arthritis care & research 2014; 66: 1867-1872.
35. Parvizi J, Pour AE, Hillibrand A, Goldberg G, Sharkey PF, Rothman RH. Back pain and total hip arthroplasty: a prospective natural history study. Clin Orthop Relat Res 2010; 468: 1325-1330.

36. Brinks A, van Rijn RM, Willemsen SP, Bohnen AM, Verhaar JA, Koes BW, et al. Corticosteroid injections for greater trochanteric pain syndrome: a randomized controlled trial in primary care. Ann Fam Med 2011; 9: 226-234.

Summary

Summary

The aim of the research described in this thesis was to assess the effectiveness of intramuscular corticosteroid injection in patients with painful hip osteoarthritis (OA), and to gain insight in the course of pain and comorbidities influencing hip complaints in patients with hip OA.

In **chapter 2** the study protocol of our double-blinded, randomized controlled trial (RCT) is presented. We enrolled patients (aged > 40 years) with painful hip OA scoring ≥3 on an 11-point numerical rating scale (NRS:0-10;0=no hip pain) despite the use of oral analgesics. Patients were screened for eligibility by general practitioners and orthopaedic surgeons. Patients were randomized to receive either 40mg of triamcinolone acetate or placebo (saline) with an intramuscular injection into the ipsilateral gluteus muscle.

Randomization was stratified for setting (primary care versus secondary care). To assure blinding an independent pharmacy assistant allocated each included patient based on a computerized randomization list. After randomization the vials for the injections were prepared, packed and sealed in an identical way for both groups by the pharmacy assistant. An independent trial nurse not involved with follow-up measurements prepared and administered the injection out of sight of the patient, assessors, treating doctors, and researchers.

The primary outcome was severity of hip pain at 2 weeks, measured with an 11-point numerical rating scale (NRS: 0-10, where 0=no pain) in rest and on walking, and with the Western Ontario and McMaster University Osteoarthritis Index pain subscale (WOMAC pain: 0 to 100, where 0 equals no symptoms). Secondary outcomes were the primary outcomes at 4, 6, and 12 weeks follow-up. Additional secondary outcome measures were WOMAC function, stiffness and total, quality of life (EQ-5D), Intermittent and Constant Osteoarthritis Pain (ICOAP), and patients' perceived recovery, using a 7-point Likert scale. Statistical analysis was based on the intention-to-treat principle. Linear mixed models with repeated measures were used for continuous outcomes. Generalized estimating equations analyses (GEE) with repeated measures were done for dichotomous outcomes.

In **chapter 3** the results of this performed RCT are shown. 107 patients were randomized of which 106 patients could be analyzed; 52 patients in the corticosteroid group and 54 patients in the placebo group. At 2 weeks follow-up, the corticosteroid injection was statistically significant and clinically relevant associated with hip pain reduction at rest (difference -1.3, 95%CI -2.3 to -0.3) compared to the placebo injection. At 4, 6 and 12 weeks the corticosteroid injection was also associated with statistically significant and clinically relevant hip pain reduction at rest as well as during walking. Moreover, at almost all follow-up measurements the estimates showed statistically significant and clinically relevant differences in favor of the corticosteroid injection on WOMAC function, stiffness, and total, and ICOAP. No significant differences between groups were found for side effects and quality of life. At 2 weeks follow-up perceived improvement and the OMERACT-OARSI responders showed a significant effect

in favor of corticosteroid injection, OR 2.8 (95%CI 1.3 to 6.4 and OR 3.9 (95% CI 1.2 to 7.2) respectively.

We conclude that an intramuscular corticosteroid injection compared to placebo showed clinical effectiveness in patients with painful hip OA for at least 12 weeks of follow-up.

Chapter 4 systematically outlines the diagnostic value of intra-articular anesthetic hip injection in patients with hip pain atypical for OA. A systematic literature search was conducted until end December 2011. Studies assessing the diagnostic value of anesthetic hip injections in differentiating between pain caused by OA or another source were included and a meta-analysis was performed. Of the 1387 potentially eligible articles, nine case series with high risk of bias were included. The data of seven studies (351 participants) could be pooled to calculate pooled estimates of sensitivity, specificity, and likelihood ratios. The pooled sensitivity was 0.97 (95% CI 0.87 - 0.99). Pooled specificity was 0.91 (95% CI 0.83 - 0.95). The positive likelihood ratio was 10.6 (95% CI 5.6 - 20.1) and the negative likelihood ratio was 0.04 (95% CI 0.01 - 0.15).

Although all studies used total hip replacement (THR) as reference standard, all studies had partial verification bias. In our pooled analyses, 75% of patients that had a good response to the diagnostic injection received a THR, compared to 15% of patients that had a negative response to the diagnostic injection. We conclude therefore that for clinical practice, no recommendation can be made regarding the use of hip injections for diagnosing hip OA. High quality, accurately reported studies are needed to provide better evidence on the diagnostic role of hip injection.

In **chapter 5** a cohort study assessing the association between two cartilage biomarker and clinical symptoms in patients with hip OA using pain trajectories defined by Latent Class Growth Analysis (LCGA) is reported. LCGA is a statistical technique that has the ability to find groups of people who are similar in their responses to measured variables, e.g., pain scores. We used a longitudinal dataset of patients with hip OA (n=222) where LCGA was applied. This resulted in five different pain trajectories over a 2-year period of follow-up, i.e., high pain, moderate pain, mild pain, regularly progressive pain and highly progressive pain. We selected two biomarkers of interest: uCTXII and uCIIM. Both these markers are derivates of type II collagen and degraded by enzymes during cartilage erosion and are excreted in urine.

The objective was to assess associations between uCTX-II or uCIIM and severity of hip pain in patients with mild or moderate hip OA over a 2-year period, and establish whether the level of these biomarkers at baseline could estimate a specific trajectory of hip pain. Urinary biomarkers and symptom severity were measured 6-monthly with a 2-year follow-up. Patients were recruited from general practices. The primary outcome was hip pain, measured with the WOMAC subscale and the Visual Analogue Scale (VAS). LoguCTX-II and loguCIIM were not associated with WOMAC pain or VAS pain during the 2-year follow-up. Patients in the highly progressive pain trajectory and the moderate pain trajectory were more likely to

have a higher loguCTX-II at baseline (OR 6.7; 95% CI 1.6-28.2 and OR 4.8; 95% CI 1.0-22.8, respectively) than patients in the mild pain trajectory.

In conclusion in patients with mild or moderate pain due to hip OA the urinary biochemical markers uCTX-II and uCIIM are not cross-sectionally associated with hip pain at 6 month-intervals during the 2-year follow-up.

Chapter 6 starts with a systematic outline of available literature on associations between weather conditions and pain in OA. This resulted in 11 studies assessing different weather variables, e.g. temperature, barometric pressure, precipitation and relative humidity. None of the meteorological variables showed a consistent correlation with patients' pain in OA.

Secondly we assessed whether there is an association between ambient weather conditions and patients' clinical symptoms in patients with hip OA. We used a cohort study with a 2-year follow-up and 3-monthly measurements and prospectively collected data on weather variables. The study population consisted of 222 primary care patients with hip OA. Weather variables included temperature, wind speed, total amount of sun hours, precipitation, barometric pressure, and relative humidity. The primary outcomes were severity of hip pain and hip disability as measured with the WOMAC pain and function subscales. On the day of questionnaire completion, mean relative humidity was associated with WOMAC pain (estimate 0.1; 95% CI 0.0–0.2; p 0.02). Mean barometric pressure was associated with WOMAC function (estimate 0.1; 95% CI 0.0–0.1; p 0.02). The other weather variables were not associated with the WOMAC pain or function score. However, the contribution of these weather variables in the pain score or function score was small. An increase of 10% in relative humidity increased the WOMAC pain score by 1 on a scale of 0 to 100. In addition to this, the range of relative humidity in our database was 49% to 99%, which corresponds to a maximum change in pain score of 5 on a scale of 0 to100. Similarly, for each 10-hPa increase in barometric pressure, the WOMAC function score deteriorates by 1 point on a scale of 0 to 100. The range of barometric pressure in our database was 980.4 to 1041.7, resulting in a maximum change in function score of 6.1 on a scale of 0 to 100. Relative humidity contributed <1% to the explained within-patient variance and between-patient variance of the WOMAC pain score. Barometric pressure contributed <1% to the explained within-patient variance and between-patient variance of the WOMAC function score.

Our results support the general opinion of OA patients that barometric pressure and relative humidity influence perceived OA symptoms. However, the contribution of these weather variables to the severity of OA symptoms was not clinically relevant.

In **chapter 7** we investigated the prevalence of Greater Trochanter Pain Syndrome (GTPS) in patients with hip OA and whether the co-existence of GTPS is associated with perceived hip pain in these patients.

Here we used a cohort of 222 patients with hip OA recruited from general practices with a follow-up of 2 year. GTPS was diagnosed by physical examination at baseline and at 2-year follow-up. GTPS was defined as tenderness at or around the greater trochanter, recognition

of this tenderness as one of the complaints, and a painful resisted hip abduction. Primary outcome was hip pain severity measured with the WOMAC subscale for hip pain (0-100; 0 equals no pain,) and the VAS (0-100; 0 equals no pain). GTPS was present in 32/205 (16%) patients at baseline and in 26/184 (14%) patients at follow-up. Eight (4%) patients had GTPS at both baseline and follow-up. GTPS was associated with WOMAC pain (estimate 10.2, 95% CI 4.3-16.1; p=0.001) and VAS pain (estimate 13.8, 95% CI 7.0-20.6; p<0.001).

In conclusion, one in seven patients with hip OA had concurrent GTPS. Patients with hip OA and GTPS showed clinically significant higher hip pain scores than those with hip OA without GTPS.

Chapter 8 presents the main findings of this thesis in relation to existing evidence and their additional clinical value. Besides we reflect in this chapter on study limitations and their implications for daily clinical practice and future research.

Samenvatting (Dutch summary)

Samenvatting (Dutch summary)

Het doel van het onderzoek beschreven in dit proefschrift was de effectiviteit van een intramusculaire corticosteroïdinjectie bij patiënten met pijnlijke heupartrose te onderzoeken. Daarnaast wilden we inzicht krijgen in het pijnbeloop en comorbiditeiten die heupklachten beïnvloeden bij patiënten met heupartrose.

In **hoofdstuk 2** presenteren wij het studieprotocol van onze dubbelblinde, gerandomiseerde, gecontroleerde trial (RCT). Patiënten (> 40 jaar) werden geworven voor ons onderzoek als zij pijnlijke heupartrose hadden ondanks gebruik van orale analgetica met een score van ≥3 op een 11-punts Numerical Rating Scale (NRS:0-10;0=geen pijn). Patiënten werden gescreend op geschiktheid door huisartsen en orthopaedisch chirurgen. Vervolgens werden patiënten gerandomiseerd om ofwel 40mg triamcinolonacetaat ofwel placebo (zoutoplossing) te ontvangen via een intramusculaire injectie in de ipsilaterale bilmusculatuur.

De randomisatie was gestratificeerd voor setting (eerstelijn versus tweede lijn). Om zeker te zijn van blindering werd iedere patiënt een behandeling toegewezen door een onafhankelijke apothekersmedewerker met behulp van een geautomatiseerde randomisatielijst. Na randomisatie werden de flacons voorbereid, verpakt en verzegeld op identieke wijze voor beide groepen door de apothekersmedewerker. Een onafhankelijke onderzoekmedewerker, die verder niet betrokken was bij de vervolgmetingen, maakte de injecties klaar en diende deze toe, buiten het zicht van patiënt, behandeld artsen en onderzoekers.

De primaire uitkomst was ernst van heuppijn na 2 weken, gemeten met een 11-punts Numerical Rating Scale (NRS:0-10;0=geen pijn) in rust en tijdens lopen, en met de Western Ontario and McMaster University Osteoarthritis Index pijn subschaal (WOMAC pijn: 0-100, 0=geen pijn). De secundaire uitkomstmaten zijn de primaire uitkomstmaten na 4, 6 en 12 weken. Andere secundaire uitkomstmaten zijn WOMAC functie, stijfheid en totaalscore, kwaliteit van leven (EQ-5D), intermitterende en constante artrose pijn (Intermittent and Constant Osteoarthritis Pain (ICOAP)) en het door de patiënt ervaren herstel, gemeten met een 7-punts Likert schaal. Statistische analyse was gebaseerd op het intention-to-treat principe. Continue uitkomsten werden geanalyseerd met linear mixed models met herhaalde metingen. Dichotome uitkomsten werden geanalyseerd met generalized estimating equations analyses (GEE) met herhaalde metingen.

In **hoofdstuk 3** laten we de resultaten van bovengenoemde RCT zien. Er werden 107 patiënten gerandomiseerd, waarvan wij 106 patiënten konden analyseren. De corticosteroïdgroep bestond uit 52 patiënten, de placebo-groep uit 54 patiënten. Na 2 weken was de corticosteroïdinjectie statistisch significant en klinisch relevant geassocieerd met vermindering van heuppijn in rust (verschil -1,3; 95% betrouwbaarheidsinterval (BI) -2,3 tot -0,3) in vergelijking met de placebo-injectie. Na 4, 6 en 12 weken was de corticosteroïdinjectie ook statistisch significant en klinisch relevant geassocieerd met vermindering van heuppijn in rust en tijdens lopen. Bovendien toonde de corticosteroïdinjectie op bijna alle vervolgmo-

menten een statistisch significant en klinisch relevant verschil voor WOMAC functie, stijfheid, totaal en ICOAP. Er werden geen significante verschillen gevonden tussen de groepen voor bijwerkingen en kwaliteit van leven. Na 2 weken toonde het ervaren herstel en de OMERACT-OARSI responders een significant effect ten faveure van corticosteroïdinjectie (OR 2,8 (95%BI 1,3 tot 6,4 respectievelijk OR 3,9 (95%BI 1,2 tot 7,2).

We concluderen dat een intramusculaire corticosteroïdinjectie vergeleken met een placebo-injectie klinisch effectief is voor patiënten met pijnlijke heupartrose gedurende minimaal 12 weken.

In **Hoofdstuk 4** bekeken we met een systematisch literatuur overzicht de diagnostische waarde van intra-articulaire heupmarcaïnisatie voor patiënten met heuppijn die atypisch is voor artrose. Literatuur werd systematisch doorzocht tot eind december 2011. We includeerden artikelen van studies die de diagnostische waarde van intra-articulaire heupmarcaïnisatie onderzochten en voerden een meta-analyse uit. Van de 1387 potentieel geschikte artikelen werden 9 artikelen geïncludeerd die 9 case series met hoog risico op vertekening beschreven. De gegevens van 7 onderzoeken met in totaal 351 patiënten konden worden samengevoegd om gepoolde schatters van sensitiviteit, specificiteit en likelihood ratios te berekenen. De gepoolde sensitiviteit was 0.97 (95%BI 0.87 tot 0.99). De gepoolde specificiteit was 0.91 (95%BI 0.83 tot 0.95). De positieve likelihood ratio was 10.6 (95%BI 5.6 tot 20.1) en de negatieve likelihood ratio 0.04 (95%BI 0.01 tot 0.15).

Hoewel alle onderzoeken totale heupprothese (THP) als referentie standaard gebruikten, hadden alle onderzoeken gedeeltelijke verificatie bias. In onze gepoolde analyses kreeg 75% van de patiënten met een goede respons op de diagnostische injectie een THP, vergeleken met 15% van de patiënten met een negatieve respons op de diagnostische injectie. We concluderen daarom dat er voor de klinische praktijk geen aanbeveling gedaan kan worden over het gebruik van heupmarcaïnisatie om heupartrose te diagnosticeren. Onderzoek met een laag risico op vertekening is nodig om de diagnostische rol van heupmarcaïnisatie nader te bepalen.

In **hoofdstuk 5** wordt een cohortonderzoek besproken waarin de associatie tussen 2 kraakbeen biomarkers en klinische symptomen van patiënten met heupartrose is bestudeerd. Hiervoor werd gebruik gemaakt van pijntrajecten gedefinieerd door een Latent Class Growth Analysis (LCGA). Dit is een statistische techniek die groepen maakt van mensen die gelijk zijn in hun respons op gemeten variabelen, bijvoorbeeld pijnscores. We hebben een longitudinale dataset van patiënten met heupartrose (n=222) gebruikt waarop LCGA was toegepast. Dit resulteerde in 5 verschillende pijntrajecten gedurende een periode van 2 jaar follow-up. Het betreft: veel pijn, matige pijn, milde pijn, geleidelijk toenemende pijn en snel toenemende pijn. Beide onderzochte kraakbeen biomarkers, uCTXII en uCIIM, zijn afbraakproducten van type II collageen en worden enzymatisch afgebroken tijdens kraakbeenslijtage. Beiden worden uitgescheiden via de urine.

Het doel van dit onderzoek was de associatie te onderzoeken tussen uCTX-II of uCIIM en de ernst van heuppijn bij patiënten met milde tot matige heupartrose gedurende 2 jaar follow-up. Daarnaast onderzochten wij of de hoogte van deze biomarkers aan het begin van het onderzoek een specifiek pijntraject kon voorspellen. Biomarkers gemeten in de urine en ernst van de symptomen werd elke 6 maanden gemeten gedurende 2 jaar. Patiënten werden geworven via huisartspraktijken. De primaire uitkomst was heuppijn, gemeten met de WOMAC pijnschaal en de Visual Analogue Scale (VAS).

LoguCTX-II en loguCIIM waren niet geassocieerd met WOMAC pijn of VAS tijdens de 2 jaar follow-up. Patiënten in het snel toenemende pijntraject en patiënten in het matige pijntraject hadden vaker een hoge loguCTX-II aan het begin van het onderzoek OR 6.7; 95%BI 1.6 tot 28.2 en OR 4.8; 95%BI 1.0 tot 22.8, respectievelijk) dan patiënten in het milde pijntraject.

Concluderend, bij patiënten met milde tot matige pijn door heupartrose zijn de biomarkers uCTX-II en uCIIM niet cross-sectioneel geassocieerd met heuppijn gedurende 2 jaar follow-up met intervallen van 6 maanden.

Hoofdstuk 6 begint met een systematische samenvatting van de literatuur over associaties tussen weercondities en pijn bij patiënten met artrose. Dit resulteert in 11 onderzoeken die verschillende weersvariabelen bestuderen zoals temperatuur, barometerdruk, neerslag en relatieve luchtvochtigheid. Geen enkele van deze meteorologische variabelen laat een consistente correlatie zien met pijn bij artrosepatiënten.

Vervolgens hebben we gekeken of er een associatie is tussen weersvariabelen en klinische symptomen van patiënten met heupartrose. Hiervoor gebruikten we een cohort met 2 jaar follow-up en 3-maandelijkse metingen en prospectief verzamelde gegevens over weersvariabelen. De studiepopulatie bestond uit 222 eerstelijns-patiënten met heupartrose. De bestudeerde weersvariabelen waren temperatuur, windsnelheid, totale hoeveelheid zonuren, neerslag, barometerdruk en relatieve luchtvochtigheid. De primaire uitkomsten waren de ernst van heuppijn en de heupfunctie gemeten met de WOMAC pijn en WOMAC functie vragenlijsten. Op de dag van invullen van de vragenlijst was WOMAC pijn geassocieerd met relatieve luchtvochtigheid (schatter 0.1; 95%BI 0.0 tot 0.2; P .02). De bijdrage van de weersvariabele aan de pijnscore was echter klein. Een toename van 10% in relatieve luchtvochtigheid gaf een toename van de WOMAC pijnscore van 1 op een schaal van 0 tot 100. Bovendien, was de range van relatieve luchtvochtigheid in onze data tussen de 49% en 99%, wat overeenkomt met een maximum verschil in pijnscore van 5 op en schaal van 0 tot 100.

Gemiddelde barometerdruk was geassocieerd met WOMAC functie (schatter 0.1; 95%BI 0.0 tot 0.1; P .02). Ook voor barometerdruk geldt dit kleine verschil. Voor elke 10 hPa toename in barometerdruk, verslechtert de WOMAC functiescore met 1 punt op een schaal van 1 tot 100. De range van barometerdruk in ons databestand was 980.4 tot 1041.7, wat resulteert in een maximum verschil in functiescore van 6.1 op een schaal van 0 tot 100.

Relatieve luchtvochtigheid droeg <1% bij aan de verklaarde binnen-patiënt variantie en tussen-patiënt variantie voor de WOMAC pijnscore. Barometerdruk droeg <1% bij aan de ver-

klaarde binnen-patiënt variantie en tussen-patiënt variantie voor de WOMAC functiescore. De andere weersvariabelen waren niet geassocieerd met WOMAC pijn of WOMAC functie.

Onze resultaten ondersteunen de algemene opinie van patiënten met artrose dat barometerdruk en relatieve luchtvochtigheid de symptomen van artrose beïnvloeden. Maar de bijdrage van deze weersvariabelen aan de ernst van symptomen van artrose was klinisch niet relevant.

In **hoofdstuk 7** onderzochten we de prevalentie van het Trochanter Major Pijn Syndroom (ook wel Greater Trochanter Pain Syndrome (GTPS) genoemd) bij patiënten met heupartrose. Daarnaast bestudeerden we of aanwezigheid van GTPS geassocieerd is met heuppijn bij patiënten met heupartrose.

Hiervoor gebruikten we een cohort van 222 patiënten met heupartrose die geworven waren in de huisartsenpraktijk. Deze patiënten werden 2 jaar gevolgd. GTPS werd gediagnosticeerd door lichamelijk onderzoek aan het begin van het onderzoek en na 2 jaar follow-up. GTPS werd gedefinieerd als gevoeligheid op of rond het trochanter major, herkenning van de gevoeligheid als een van de klachten en pijnlijke heupadbuctie tegen weerstand in. Primaire uitkomst was ernst van de heuppijn gemeten met de WOMAC pijn subschaal (0-100; 0 = geen pijn) en de VAS (0-100; 0 = geen pijn).

GTPS was aanwezig in 32/205 (16%) patiënten bij het begin van het onderzoek en in 26/184 (14%) van de patiënten na 2 jaar follow-up. Acht (4%) patiënten hadden GTPS zowel bij begin van het onderzoek als na 2 jaar. GTPS was geassocieerd met WOMAC pijn (schatter 10,2; 95%BI 4.3 tot 16.1; p 0.001) en VAS pijn (schatter 13.8, 95%BI 7.0 tot 20.6; p<0.001).

Concluderend, één op de zeven patiënten met heupartrose had tegelijkertijd GTPS. Patienten met heupartrose en GTPS hadden klinisch significant hogere pijnscores dan patiënten met heupartrose zonder GTPS.

In **hoofdstuk 8** zijn de belangrijkste bevindingen van dit proefschrift uiteengezet in relatie tot de bestaande literatuur en hun toegevoegde waarde hierop. Daarnaast wordt er in dit hoofdstuk gereflecteerd op de beperkingen van het onderzoek en de implicaties voor de praktijk en toekomstig wetenschappelijk onderzoek.

Dankwoord

Dankwoord

Onderzoek doe je niet alleen en ik heb de afgelopen jaren met veel mensen mogen samenwerken. Graag wil ik iedereen bedanken die een bijdrage heeft geleverd aan dit proefschrift. Een aantal mensen wil ik in het bijzonder bedanken.

Mijn promotor, prof. dr. SMA Bierma-Zeinstra. Beste Sita, dank dat je mij, met destijds vooral klinische ervaring, op dit onderzoeksproject durfde aan te nemen. Jij hebt mij laten zien dat onderzoek doen ongelofelijk leuk is. Dankzij jouw voortvarende aanpak lagen er na 2,5 jaar 4 manuscripten. Dank ook dat je me de tijd hebt gegeven voor het afronden van HOCI naast mijn opleiding.

Mijn copromotoren, dr. PAJ Luisterburg en dr. PK Bos.

Beste Pim, dank voor je begeleiding van mijn promotietraject. Je hebt mij de ruimte gegeven tijdens mijn onderzoek, maar daarnaast was je laagdrempelig beschikbaar als ik vast liep. Je nuchtere adviezen zorgden altijd weer voor genoeg voortgang in het geheel. Dank ook dat je de laatste 3 jaar zoveel 'over de mail' hebt willen doen. Ik heb onze samenwerking als zeer prettig ervaren.

Beste Koen, grote dank voor je klinische blik. Fijn dat jij in je commentaar op mijn manuscripten altijd weer vroeg: 'maar wat heeft de clinicus hier nu aan'. Dit heeft de artikelen beter leesbaar en praktischer toepasbaar gemaakt. Dank ook voor het tussen de bedrijven door scoren van alle röntgenfoto's voor HOCI. Ik hoop dat we in de toekomst nog een mooi hip-spine cohort kunnen opzetten.

Collega's van de afdeling huisartsgeneeskunde; een grote groep onderzoekers, onderzoeksmedewerkers en AIOTHO's. Dank voor de gezelligheid, de maandag-lunch-haalwandelingen naar de Appie, de vele koffie- en zelfgebakken taart-momenten, de ijsjes op het Westzeedijkbalkon en de mooie nevenactiviteiten tijdens congressen.

Speciale dank aan Rianne R. voor het gebruik van de GOAL data en je altijd snelle antwoord op mijn vragen over GOAL. Ook dank aan Rianne vd H. voor het waarnemen van de honneurs tijdens mijn verlof.

Marlous, Saskia, Jantine en Pauline, jullie onderzoeken liepen al toen ik begon. Dank voor alle voorbeelden die ik van jullie mocht lenen: van METC-aanvraag tot query voor internetvragenlijst.

Mijn kamergenoten straatzijde van de eerste kamer van de WZD: Marienke, Gijs en Marijke, dank voor de gezellige breaks tijdens het onderzoek doen.

Marlies, dank voor je secretariële ondersteuning tijdens mijn project. Jan, dank voor je tijd en uitleg over internetvragenlijsten, datasystemen, databeheer en query's.

Mariet, dank voor je inzet voor het HOCI-project. Includeren bij huisartsen, dubbel-blinde injecties toedienen, administratie of het controleren van steekproeven, als er een SOPje van was, ging jij aan de slag. Fijn ook dat je samen met Metthilde het HOCI project zo goed hebt

voorgezet na mijn vertrek. Dank ook voor je interesse in het thuisfront. Geniet van je (pre) pensioen samen met Dre.

Beste prof. Verhaar, dank dat ik wekelijks een deel van mijn onderzoekstijd mocht doorbrengen bij de klinisch onderzoekers orthopaedie. Dit is de voortgang van het HOCI-project zeker ten goede gekomen. Dank ook voor suggesties en kritische blik op mijn manuscripten.

Collega's van de afdeling klinisch onderzoek orthopaedie. Belle, Vincent, Eline, Max, Guus, Tijs, Job, Maaike, dank voor jullie gastvrijheid in HS-104 en het ortho-biebje. Ik heb het enorm naar mijn zin gehad op mijn woensdag ortho-dag. Hard werken werd bij jullie afgewisseld met de nodige humor, voetbal-weetjes, gezellige etentjes en sportieve uitjes.

Belle, fijn dat je nu helemaal op je plek bent bij de sportgeneeskunde. Naast een harde werker ben je zeer sociaal en altijd bereid om te helpen.

Vincent, lotgenoot als het gaat om tegenvallende inclusies. Dank voor je gezelligheid, goede koffie en relativeringsvermogen ('kaftje erom en klaar'). Mijn kaftje zit erom, hopelijk volgt die van jou ook snel.

Eline, dank voor je hulp bij logistieke zaken. Jouw kennis van de juiste wegen op de polikliniek orthopaedie zorgde ervoor dat ik op de goede plek mijn HOCI-bakje kreeg.

Guus, ik was er meestal als jij er niet was. Dus vooral dank voor het gebruik maken van je bureau.

Tijs, Job en Maaike, dank voor de gezelligheid. Max, dank voor je adviezen over multicenter onderzoek en je kritische blik op het HOCI-onderzoek.

Orthopaeden Isala Zwolle: dr. Verheijen, dr. Zuurmond, dr. Tulp, dr. Mostert, dr. Janus, dr. Ettema, drs. van Solinge en drs. van Egmond. Dank voor jullie interesse in mijn promotietraject en de tijd die ik voor de afronding hiervan heb gekregen. Dank ook voor het prettige opleidingsklimaat.

Orthopaedie collega's Zwolle: Arjan, Arina, Chris, Edwin, Erwin, Frank, Jelle, Jeroen, Nienke, Maurits, Marije, Patricia, Paul, Rob, Stefan, Thomas, Wybren, Wouter, Wietse. Een mooie en gezellige groep. Dank voor jullie interesse, support, tips om mijn presentaties te verbeteren en luisterende oren. Arina, dank voor de tip voor de voorkant van dit boekje.

Dit proefschrift kan niet verdedigd worden zonder de steun van mijn paranimfen.

Metthilde, dank voor al het werk dat je hebt verzet voor het HOCI-project. Ik besef goed dat ik het enorm getroffen heb met een ervaren onderzoeksassistente. Dankzij jou kon ik al snel de administratie rondom HOCI los laten en gaan werken aan andere dingen. Fantastisch hoe jij en Mariet het project zo hebben voortgezet na mijn vertrek. Dank ook voor je gezelligheid, nuchtere kijk en 'moederlijke' adviezen over van alles. Fijn dat je naast me wilt staan tijdens mijn promotie. De stellingen zijn in het Nederlands, dus maak je daarover geen zorgen!

Jeroen, mijn 'kleine' broer. Dank voor alle kopjes thee die je in Breda na het tennissen kwam halen. Dank ook voor je rust als ik weer eens doordraaf. Ik vind het mooi hoe je samen met Nienke je toekomst uitstippelt. Hoewel we tegenwoordig wat verder uit elkaar wonen blijven we elkaar hopelijk vaak zien.

Pap en mam, jullie hebben me alle mogelijkheden en vrijheid gegeven met te ontwikkelen. Bedankt voor jullie steun bij mijn keuzes. Mam, dank voor het tijdelijke, gezellige, onderdak en het oppassen op Annemarijn tijdens mijn laatste maanden in Rotterdam. Sietske, mijn kleine zusje, fantastisch dat jij de grote reizen, waar ik stiekem van droom, gewoon maakt.

Henk en Nel, ik heb geluk met schoonouders zoals jullie. Dank voor de oppasdagen op de kleintjes, zodat ik meters kon maken.

Alle (schoon)familie en vrienden, gelukkig is er meer dan alleen onderzoek doen. Dank voor de nodige afleiding en gezelligheid.

Maarten, dank voor je onvoorwaardelijke steun, liefde, humor en relativeringsvermogen. Dank ook dat je af en toe op de rem trapt. Ik geniet van elk moment samen. Piu bella cosa.

Annemarijn, mamma vindt het heel gezellig als jij op zolder komt kleuren of spelen terwijl ik druk ben op de 'konkjoeter'. Floris, jouw vrolijkheid is aanstekelijk. Lieve Annemarijn en Floris, mamma's boek is natuurlijk ongelofelijk saai: veel tekst, weinig plaatjes. Misschien lezen jullie het later eens, als jullie groot zijn. Vanavond lees ik jullie gewoon weer voor uit Kikker, Pluk of Floddertje.

Curriculum Vitae

Curriculum Vitae

Desirée Maria Johanna Dorleijn is op 16 juli 1982 geboren in Vlissingen. Na het behalen van haar gymnasium diploma aan de Christelijke Scholengemeenschap Walcheren in Middelburg begon zij in 2000 met de studie geneeskunde aan de Universiteit Utrecht.

Na afronding van haar studie in 2006 werkte zij als arts-assistent op de spoedeisende hulp en bij de chirurgie en orthopaedie in verschillende ziekenhuizen (Beatrixziekenhuis, UMC St Radboud, Tweesteden Ziekenhuis, IJssellandziekenhuis).

In januari 2011 begon zij als promovendus aan het Erasmus Medisch Centrum onder supervisie van prof. dr. S.M.A. Bierma-Zeinstra. Zij werkte aan de in dit proefschrift beschreven projecten over heupartrose, waaronder het HOCI-onderzoek. Dit is een gerandomiseerd, gecontroleerd onderzoek bij patiënten met heupartrose naar het systemisch effect van corticosteroïden op pijnklachten.

In oktober 2013 startte zij haar vooropleiding chirurgie in de Isala te Zwolle (opleider dr. S.H. van Helden). Sinds oktober 2015 werkt zij als AIOS orthopaedie in Isala (opleider dr. C.C.P.M. Verheijen, Isala; prof. dr. S.J. Bulstra, UMC Groningen). Zij vervolgt haar opleiding per januari 2017 in het Medisch Centrum Leeuwarden (opleider dr. P.C. Rijk).

Daarnaast is zij sinds januari 2016 lid van de ledenraad van de ANWB. Desirée is getrouwd met Maarten Kiel en samen hebben zij 2 kinderen: Annemarijn en Floris.

PhD Portfolio

PhD Portfolio

Summary of PhD training and teaching

Name PhD student:	Desirée Dorleijn
Erasmus MC Department:	General Practice
Research school:	NIHES
PhD period:	2011-2016
Supervisor:	Prof.dr. S.M.A. Bierma-Zeinstra
Co-supervisors:	Dr. P.A.J. Luijsterburg
	Dr. P.K. Bos

PhD Training	Year	Workload Hours / ECTS
Courses		
Course Endnote, Erasmus MC Library	2011	2 hours
Course systematic literature search, Erasmus MC Library	2011	2 hours
Good Clinical Practice (BROK)	2011	30 hours
Introduction to clinical research, NIHES	2012	0.9 ECTS
Biostatistics for clinicians, NIHES	2012	1.0 ECTS
Regression analysis for clinicians, NIHES	2012	1.9 ECTS
Courses for the quantitative researcher, NIHES	2012	1.4 ECTS
Repeated Measurement, NIHES	2012	1.4 ECTS
Biomedical English Writing and Communication	2012	4.0 ECTS
Recertification Good Clinical Practice	2015	4 hours
Seminars and workshops		
Minisymposium 'Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen'	2011	8 hours
PhDay: Get the best out of your PhD	2011	4 hours
Presentations		
Oral		
NOF, 56th Northern Orthopaedic Federation Congress, Tallinn, Estland	2012	20 hours
ROGO-dag Rotterdam, Rotterdam	2012	10 hours
NOF, 58th Northern Orthopaedic Federation Congress, Linkoeping, Sweden	2016	20 hours
Dutch Orthopaedic Association 'NOV' najaarsvergadering, Veldhoven	2016	20 hours
Poster		
OARSI, world congress on Osteoarthritis, San Diego, USA	2011	16 hours
OARSI, world congress on Osteoarthritis, Philadelphia, USA	2013	16 hours
OARSI, world congress on Osteoarthritis, Amsterdam, the Netherlands	2016	16 hours
Teaching		
Supervising 'critical appraisal of biomedical article for medical students' (3 times)	2012, 2013	9 hours
Supervising medical student writing letter-to-the-editor	2012	2 hours

List of publications

List of publications

This thesis

DMJ Dorleijn, PAJ Luijsterburg, M Reijman, M Kloppenburg, JAN Verhaar, PJE Bindels, PK Bos, SMA Bierma-Zeinstra. Intramuscular corticosteroid injection versus placebo injection in hip osteoarthritis: a 12- week blinded randomized controlled trial. *Submitted*

DMJ Dorleijn, PAJ Luijsterburg, A Brinks, RM Rozendaal, A Burdorf, BW Koes, JAN Verhaar, PK Bos, SMA Bierma-Zeinstra. Greater trochanter pain syndrome: prevalence and influence on hip pain severity in patients with hip osteoarthritis in a cohort study. *Submitted*

DMJ Dorleijn, PAJ Luijsterburg PA, AC Bay-Jensen, AS Siebuhr, MA Karsdal, R. Rozendaal, PK Bos, SMA Bierma-Zeinstra. Association between biochemical cartilage markers and clinical symptoms in patients with hip osteoarthritis: cohort study with 2-year follow-up. *Osteoarthritis Cartilage* 2015, Jan 23(1): 57-62

DMJ Dorleijn, PAJ Luijsterburg, SMA Bierma-Zeinstra, PK Bos. Is Anesthetic Hip Joint Injection Useful in Diagnosing Hip Osteoarthritis? A Meta-Analysis of Case Series. *J of Arthroplasty* 2014, Jun 29(6): 1236-1242

DMJ Dorleijn, PAJ Luijsterburg, A Burdorf, RM Rozendaal, JAN Verhaar, PK Bos, SMA Bierma-Zeinstra. Associations between weather conditions and clinical symptoms in patients with hip osteoarthritis: A 2-year cohort study. *Pain* 2014, Apr 155 (4): 808–813

DMJ Dorleijn, PAJ Luijsterburg, M Reijman, M Kloppenburg, JAN Verhaar, PJE Bindels, PK Bos, SMA Bierma-Zeinstra. Effectiveness of intramuscular corticosteroid injection versus placebo injection in patients with hip osteoarthritis: design of a randomized double-blinded controlled trial. *BMC Musculoskeletal Disorders* 2011, Dec 12;12(1): 280

Other international

M Schotanus, **DMJ Dorleijn**, AJF Hosman, RMHG Huits, PP Koopmans, JMD Galama. A patient with multifocal tabetic arthropathy, A case report and review of literature. *Sex Trans Dis* 2013, Mar 40(3): 251-257

LE Richardson, **DMJ Dorleijn**, AP Verhagen. Autograft hamstring vs patellar tendon ACL reconstruction: Letter to the editor. *Am J Sports Med* 2012, 40: NP15

R van Rijn, **DMJ Dorleijn**, B Boetes, SC Wiersma-Tuinstra, S Moonen. Missing the Lisfranc fracture: a case report and review of the literature. *J Foot Ankle Surg* 2012, Mar-Apr 51(2): 270-274

DMJ Dorleijn, TE Cohen-Overbeek, F Groenendaal, HW Bruinse, Ph Stoutenbeek. Idiopathic polyhydramnios and postnatal findings. *J Mat Fet Neonatal Med* 2009, Apr 22(4) 315-320

Other national

DMJ Dorleijn, B Boetes. Een jongen met een pijnlijke lies. *NTvT* 2012, Jan 20(1): 16

DMJ Dorleijn, R Hardeman, GJJM Muijsers. Maternale Body Mass Index en uitwendige versie bij stuitligging. *NTOG* 2009, Juni (122) 147-151

DMJ Dorleijn, A Speetgens. Patiënt met ruptuur van m. pectoralis onder sintromgebruik. *NTvT* 2009, Jan 17(1): 17-20

Heupartrose is een veelvoorkomende, chronisch ziekte die vooral voorkomt bij oudere patiënten. Vaak treden pijn en stijfheid van de heup op. Omdat heupartrose nog niet te genezen is, bestaat de behandeling uit bestrijden van symptomen. In dit proefschrift wordt de effectiviteit van een corticosteroïdinjectie in vergelijking tot een placebo-injectie in de bilspier beschreven bij patiënten met pijnlijke heupartrose. Daarnaast wordt er inzicht gegeven in het pijnbeloop en comorbiditeiten die heupklachten beïnvloeden bij patiënten met heupartrose.

Desirée Dorleijn werd geboren op 16 juli 1982 te Vlissingen. De studie geneeskunde volgde zij aan de Universiteit Utrecht. Na het behalen van haar arts-examen werkte zij als arts-assistent op de afdelingen spoedeisende hulp, chirurgie en orthopaedie. In 2011 startte zij aan het Erasmus Medisch Centrum met onderzoek onder patiënten met heupartrose afkomstig van huisartsen en orthopaeden. In een geblindeerde gerandomiseerde studie onderzocht zij of een corticosteroïdinjectie in de bilspier een vermindering van pijn geeft bij deze patiënten. Dit onderzoek vormde de basis van dit proefschrift. Zij is vanaf 2013 in opleiding tot orthopaedisch chirurg in het Isala ziekenhuis te Zwolle.