What can we do about osteoarthritis?

Lohmander, Stefan

Published in:
Arthritis Research & Therapy

DOI:
10.1186/ar74

2000

Commentary

What can we do about osteoarthritis?

L Stefan Lohmander

University Hospital, Lund, Sweden

Received: 11 January 2000
Revisions requested: 24 January 2000
Revisions received: 25 January 2000
Accepted: 31 January 2000
Published: 18 February 2000

Arthritis Res 2000, **2**:95–100

Abstract

Osteoarthritis is complex in genetics, pathogenesis, monitoring and treatment. Current treatment of osteoarthritis does not influence progression. Much could be gained by more effective 'low-tech-low-cost' treatment. However, many patients have rapidly progressive disease, multiple joint involvement, and severe disease. We need to clarify the genetics of osteoarthritis, identify those at risk for progression and severe disease, and identify molecular processes critical for joint survival and failure. Will saving the cartilage improve patient pain and function? Effective outcome measures are needed to accelerate testing of new treatments. Further improvement is needed in joint implant technology to decrease costs, wear and loosening.

Keywords: biomarkers, genetics, osteoarthritis, pathophysiology, treatment

Introduction

Joint diseases affect hundreds of millions of patients throughout the world, causing pain and disability with great impact on individuals and on society as a whole. Osteoarthritis is the most common joint disease; in the near future, it is projected to rank second for women and fourth for men in the developed countries in terms of years lived with disability [1]. Elderly patients are most often affected (joint diseases account for half of all chronic conditions in persons aged 65 years and over) and, because the number of individuals over the age of 50 years is expected to double worldwide between 1990 and 2020, the global burden of osteoarthritis will increase dramatically. In Europe by 2010 there will be more people aged over 60 years than under 20 years, and by 2020 these elderly individuals will represent 25% of the population. Unless we invest in increased research and education now to decrease the future burden of joint disease, osteoarthritis in the ageing population will generate a global avalanche of costs and disability [2].

Risk factors

Osteoarthritis is a complex disorder and has high population prevalence. It is genetically complex, because it generally lacks a clear Mendelian pattern of inheritance and is probably associated with interactions of multiple genes. The fact that disease initiation, progression and severity may be influenced by multiple environmental factors interacting with multiple variations in the genetic background adds further complexity. Furthermore, the distinction between disease and nondisease is often problematic.

Genetic factors are thus recognized as being associated with osteoarthritis, and epidemiological studies [3–10] have illustrated the influence of heredity on common forms of osteoarthritis. Further examples of a genetic predisposition for osteoarthritis are given by rare subtypes of osteoarthritis that appear to have a basis in single gene mutations and are associated with early age onset (for review [11]). Examples of mutated genes that may be responsible for these diseases include those that encode cartilage-specific colla-

gens and cartilage oligomeric matrix proteins [12–19]. Additional reports [20–23] have presented evidence for and against the association of osteoarthritis with yet other genes that may encode molecules that are related to cartilage function. The availability of DNA collections from large numbers of families and sibling pairs with osteoarthritis, coupled with novel techniques for genome-wide scans, are now identifying evidence for yet other predisposing multiple chromosomal loci for osteoarthritis [24–26].

Environmental factors interact with this variable genetic background. For example, joint malalignment, overloading (eg related to work or high body weight) and injury are recognized risk factors that predispose to osteoarthritis to varying degrees [27]. The impacts of such risk factors in different joints vary. For example, obesity in women is associated with an increased risk for knee osteoarthritis, but the effect in males and in the hip is less well established [4,28–30]. Acute injuries to the ligaments and menisci of the knee are well-recognized and common causes of osteoarthritis [31]. For example, meniscus injury followed by surgical removal is associated with a relative risk of 14 for radiological osteoarthritis, over that of age-matched and sex-matched control individuals [32]. In comparison, relative risks associated with obesity, work and other factors are more modest and usually range between 2 and 4 [27]. From a research perspective, injury-related development of osteoarthritis has the distinct advantage that the human osteoarthritis disease process can be followed from its earliest stages.

Progression of disease

Disease progression in osteoarthritis is usually slow, and occurs over years or decades. The rate of progression is variable between individuals, and many patients with clinically diagnosed osteoarthritis may not suffer appreciable progression by either symptoms or radiographic changes over long periods [33–36]. Progression may also be variable over time in the same individual, and joint destruction may occur in episodes.

The distinction between disease and nondisease is problematic in osteoarthritis, and complicates most aspects of osteoarthritis research, including epidemiology and genetics research. The ‘clinical’ definition of osteoarthritis for use in, for example, clinical trials is usually based on a defined combination of symptoms and plain radiography changes that are caused by altered joint structure. The correlation between the degree of radiological change and symptoms is weak, however, and it is common for patients with radiological osteoarthritis to have few or no symptoms, whereas classical symptoms of osteoarthritis may occur in the absence of structural changes on plain radiography [37]. The current definition of osteoarthritis needs to be operational and adapted to the purpose and tools of specific areas of research.

Pathophysiology

The osteoarthritis disease process at the tissue and cellular level is associated with destruction and loss of cartilage, remodelling of bone and intermittent inflammation. Although research focus remains on the destruction of joint cartilage, changes in subchondral bone, synovium and ligaments are detectable at an early stage in osteoarthritis. The roles played by events that take place in these tissues in the initiation and progression of osteoarthritis remain to be clarified. The complexity of the osteoarthritis process is further underlined by the increase in synthesis of cartilage matrix components that can be detected concurrently with increased degradation of cartilage matrix [38,39].

Degradation and synthesis of cartilage matrix in osteoarthritis are driven by mediators that are released by chondrocytes and synoviocytes. These mediators include cytokines (such as interleukin-1 and tumour necrosis factor), nitric oxide and growth factors [40–42]. Events that in turn may drive the increased release of these mediators include changes in chondrocyte loading that are induced by joint overload or injury [43]. These events act within a tissue environment where cartilage matrix quality and cellular reactivity may in part be determined by genetic variation. Thus, a minor insult may initiate osteoarthritis in a less resistant environment, whereas in another individual the joint may be able to compensate for a greater insult. Treatments aimed at preserving or regenerating functional tissue may be ineffective because they may be overwhelmed by mechanical processes.

Evidence suggests that synovial-derived and/or cartilage-derived proteases play a critical role in cartilage matrix degradation, with matrix metalloproteases and aggrecanases currently attracting the most attention [44–47]. Together, these proteases have the ability to degrade the major macromolecular constituents of the cartilage matrix, such as collagens, aggrecan and matrix proteins. Ultimately, elevated matrix degradation results in complete loss of the cartilage and loss in joint function. As mentioned above, the cartilage may in some situations be able to compensate for matrix loss induced by an insult. The ‘point of no return’ beyond which compensation is impossible has not been identified, but may include proteolytic damage to some part of the collagen network, or loss of critical interactions between matrix components.

Measuring osteoarthritis

Outcome measures in osteoarthritis research include patient-relevant measures, structural measures and process biomarkers in the form of molecules or molecular fragments that are released as a result of joint tissue metabolism [48–52]. Effective outcome measures are critical to many aspects of osteoarthritis research, and in particular to clinical trials of new treatments. There is no

current 'gold standard' for the diagnosis of osteoarthritis. Although ongoing clinical drug trials with osteoarthritis disease modification as the goal mostly use standardized plain radiographs to monitor structural changes in the joint, the good relationship between preservation or improvement of joint structure (eg joint space) and improvement in patient-relevant symptoms and function remains an hypothesis that is still to be proven. Magnetic resonance imaging is rapidly evolving as a method to monitor joint structure, and with time may become the preferred method to monitor this feature in osteoarthritis research and clinical trials. Similarly, osteoarthritis biomarker research is receiving increased attention as a promising modality to monitor changes in joint tissue turnover, predict osteoarthritis progression, select patients for clinical trials, and monitor response to treatment with drugs designed to prevent certain disease features, such as cartilage degradation.

Current treatments

The patient with osteoarthritis suffers from pain and loss of function. From the patient's perspective, alleviation of such features of disease is what counts, so what can we do about osteoarthritis at present?

Our current modes of treatment to decrease pain and improve functioning range from information, education, physical therapy and aids, through analgesics, non-steroidal anti-inflammatory drugs and joint injections, and to surgery in which all or part of the joint is replaced with plastic, metal or ceramic implants. The informed patient is a further critical aspect in all management approaches to chronic diseases such as osteoarthritis. The currently available treatment modalities listed above can decrease pain and improve functioning, with joint replacement in late-stage osteoarthritis perhaps being the most effective in this regard. Evidence-based reviews of current osteoarthritis treatment [53] emphasize the moderate effectiveness of many of the current treatments for osteoarthritis, however. There is no generally accepted and available means of influencing the progression of the disease, and thus all current treatment for osteoarthritis is palliative. The frequent dissociation between change in joint structure and occurrence of symptoms suggests that many first-time patients who seek medical care for joint pain will already have advanced destruction of their joint cartilage. This has implications for our ambitions to preserve cartilage by pharmacological or other interventions.

Future treatments

The above brief overview emphasizes that osteoarthritis is important from the perspective of the patient and society as a whole, and is projected to become one of the conditions with the highest impact; that current treatments often lack effectiveness; and that our understanding of the causes and disease mechanisms that are involved in osteoarthritis is incomplete.

What will we be able to do about osteoarthritis in the future? Although this commentary focuses on research that utilizes sometimes sophisticated technologies and treatments, we need to remind ourselves that much of this might not be very relevant to all of the elderly, common, 'garden-variety' patients (including those in the developing countries) with mild or moderately symptomatic osteoarthritis. Consequently, future research also needs to be directed to the development and evaluation of effective 'low technology/low cost' methods for dealing with the problems of these patients in a rational way [54]. The launch of the 'Bone and Joint Decade 2000–2010' is a timely event that will provide further support for research and education to decrease the growing global burden and cost of musculoskeletal diseases [2] (http://www.bonejointdecade.org).

What can arthritis research do about osteoarthritis for patients who are young, for those with rapidly progressive disease, for those with multiple joint involvement, and for those with severe disease? A few suggestions may be offered, looking at some of the current research questions and emerging new technologies. The genetics and epidemiology of different forms of osteoarthritis will need to be further clarified. A better understanding of the impact of environmental risk factors and their interaction with genetic background may result in possibilities for disease prevention. We need to be able to identify those patients who are at risk for progression and severe disease earlier, and we need to focus more of our attention on these patients. Molecular processes that are critical for cartilage and joint failure need to be identified. For cartilage protection, the matrix and cell features that are critical for survival of the tissue must be better understood, and crucial degradative agents, such as proteases, identified. What is the role of failed matrix synthesis and regeneration as a cause of joint failure? Will saving the cartilage improve pain and functioning? The role of local inflammation in osteoarthritis, not detected by the usual clinical signs, but by the role of cytokines, will need increased attention. More effective outcome measures are needed to accelerate testing of new treatments. Many patients with severe osteoarthritis will continue to need joint replacements; we need to improve on existing implant technology in order to decrease costs, enhance osseointegration and minimize wear, osteolysis and loosening.

Osteoarthritis is a highly prevalent, genetically complex disorder. Several large-scale investigations involving thousands of patients and genome-wide screening are now underway that are likely to identify multiple gene variations associated with an increased risk for osteoarthritis within a fairly short period. Any such variation identified in a specific population will then need to be confirmed in other populations to ascertain generalizability. The identification of specific and common genetic variations associated with

increased osteoarthritis risk will improve our understanding of the disease processes involved in osteoarthritis, and may in addition provide targets for development of new forms of treatment. It may in this context be interesting to compare the model for inheritance of osteoarthritis with that for Alzheimer's disease, in which a genetic dichotomy model is proposed [55]. In this model rare forms of inherited diseases are caused by rare, highly penetrant mutations with severe impact and early onset, whereas more common forms of the same disease that occur with increased frequency and at older age are associated with genetic risk factors in the form of common population polymorphisms. The imminent mapping of the human genome will greatly accelerate such investigations.

Further developments in molecular biology such as microarray chips allow simultaneous large-scale differential identification of thousands of genes expressed (transcriptomes) in disease [56]. This will further enhance our ability to identify molecules and processes that are relevant to osteoarthritis pathology [42], and will certainly identify additional targets for pharmacological treatment. The large number of candidate molecules and processes thus identified for testing will challenge bioinformatics research.

Industry drug discovery and development are also being revolutionized by technological advances. The application of high throughput screening, high throughput compound synthesis and rational drug design will be needed to take advantage of the exponential increase in number of potential targets. At the trial and user end pharmacogenomics aided by microarray technology, promises to provide individualized information that will aid in selection of trial patients and optimal forms of treatment for the individual.

The cost-effective monitoring of clinical trial outcomes still presents a challenge, and it has been proposed that biomarkers in osteoarthritis is an area that is now suitable for large-scale collaborative projects between industry, academic institutions and federal agencies (Osteoarthritis Initiative, http://www.nih.gov/niams/news/oisg/index.htm). It is proposed that such a collaboration could identify and evaluate biomarkers as surrogate end-points for clinical trials in osteoarthritis. If validated as surrogate end-points, use of such markers would accelerate the evaluation of new drugs in clinical trials and decrease the needed number of patients. As noted above, the potential future increase in number of drug candidates to be evaluated provides ample reason for increased efforts in this area.

The continued identification of biomarkers of osteoarthritis in the form of molecules or molecular fragments that reflect events in the diseased joint will no doubt be further accelerated by the new technologies to identify genes that are differentially expressed in disease. Such methods, in concert with proteomics and a fully mapped human genome, will likely provide a rich selection of biomarkers to test in human disease. This will, in turn, require access to large, well-characterized cohorts of patients (and control individuals) who are identified and managed by clinical investigators. Perhaps the availability of these human resources will remain the most significant bottleneck in our continued efforts to provide better treatment for osteoarthritis patients through research.

Conclusion

The genetics, pathogenesis, monitoring and treatment of osteoarthritis are complex. Evidence-based reviews point to the moderate effectiveness of current osteoarthritis treatments. There is no accepted means of influencing progression of human osteoarthritis. Although much can be gained by effective 'low technology/low cost' methods for dealing with osteoarthritis in many patients, such approaches are not appropriate for the many patients with rapidly progressive disease, multiple joint involvement and severe disease. For such patients, the genetics and epidemiology of osteoarthritis need to be further clarified. A better understanding of environmental risk factors and their interaction with genetic background may improve preventive efforts. We need to identify those who are at risk for progression and severe disease. Molecular processes that are critical for joint failure also need to be identified. For cartilage protection, the matrix and cell features that are critical for survival of the tissue must be understood and crucial degradative agents identified. What is the role of failed matrix synthesis and regeneration? Will saving the cartilage improve patient pain and functioning? The role of local inflammation in osteoarthritis needs increased attention. More effective outcome measures are needed to accelerate testing of new treatments. Many patients with severe osteoarthritis will continue to need joint replacements, and we need to improve on existing implant technology in order to decrease costs, wear and loosening.

References

1. Murray CJL, Lopez AD: *The Global Burden of Disease*. Boston: Harvard University Press, 1996.
2. Consensus document: **The Bone and Joint Decade 2000–2010 for prevention and treatment of musculo-skeletal disorders.** *Acta Orthop Scand* 1998, **69 (suppl 281)**:67–86.
3. Kellgren JH, Lawrence JS, Bier F: **Genetics factors in generalised osteoarthritis.** *Ann Rheum Dis* 1963, **22**:237–255.
4. Anderson J, Felson DT: **Factors associated with osteoarthritis of the knee in the First National Health and Nutrition Examination Survey (NHANES 1).** *Am J Epidemiol* 1988, **128**:179–189.
5. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart DJ: **Genetic influences on osteoarthritis: a twin study.** *Br Med J* 1996, **312**:940–944.
6. Chitnavis J, Sinsheimer JS, Clipsham K, *et al*: **Genetic influences in end-stage osteoarthritis. Sibling risks of hip and knee replacement for idiopathic osteoarthritis.** *J Bone Joint Surg Br* 1997, **79**:660–664.
7. Felson DT, Couropmitree NN, Chaisson CE, *et al*: **Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis. The Framingham Study.** *Arthritis Rheum* 1998, **41**:1064–1071.

8. Hirsch R, Lethbridge-Cejku M, Hanson R, *et al*: **Familial aggregation of osteoarthritis. Data from the Baltimore longitudinal study on aging.** *Arthritis Rheum* 1998, **41**:1227–1232.
9. Holderbaum D, Haqqi TM, Moskowitz RW: **Genetics and osteoarthritis.** *Arthritis Rheum* 1999, **42**:397–405.
10. Cicuttini MF, Spector DM: **The genetics of osteoarthritis.** *J Clin Pathol* 1996, **49**:617–619.
11. Jimenez S A, Williams C J, Karasick D: **Hereditary osteoarthritis.** In: *Osteoarthritis.* Edited by Brandt KD, Doherty M, Lohmander LS. Oxford University Press: Oxford, 1998:31–49.
12. Palotie A, Vaisanen P, Ott J, *et al*: **Predisposition to familial osteoarthritis linked to type II collagen gene.** *Lancet* 1989, **i**:924–927.
13. Ala-Kokko L, Baldwin CT, Moskowitz RW, Prockop DJ: **A single base mutation in the type II procollagen gene (COL2AI) as cause of primary osteoarthritis associated with mild chondrodysplasia.** *Proc Natl Acad Sci USA* 1990, **87**:6565–6568.
14. Pun YL, Moskowitz RW, Lie S, *et al*: **Clinical correlations of osteoarthritis associated with a single-base mutation (arginine519 to cysteine) in type II procollagen gene. A newly defined pathogenesis.** *Arthritis Rheum* 1994, **37**:264–269.
15. Ritvaniemi P, Korkko J, Bonaventure J, *et al*: **Identification of COLA2I gene mutation in patients with chondrodysplasias and familial osteoarthritis.** *Arthritis Rheum* 1995, **38**:999–1004.
16. Bleasel JF, Bisagnifaure A, Holderbaum D, *et al*: **Type II procollagen gene (COL2A1) mutation in exon 11 associated with spondyloepiphyseal dysplasia; tall stature and precocious osteoarthritis.** *J Rheumatol* 1995, **22**:255–261.
17. Bleasel JF, Holderbaum D, Mallock V, *et al*: **Hereditary osteoarthritis with mild spondyloepiphyseal dysplasia: are there 'hot spots' on COL2A1?** *J Rheumatol* 1996, **23**:1594–1598.
18. Bleasel JF, Holderbaum D, Brancolini V, *et al*: **Five families with arginine 519-cysteine mutation in COL2A1: evidence for three distinct founders.** *Hum Mutat* 1998, **12**:172–176.
19. Briggs MD, Hoffman SMG, King LM, *et al*: **Pseudoachondroplasia and multiple epiphyseal dysplasia due to mutations in the cartilage oligomeric matrix protein gene.** *Nature Genet* 1995, **10**:330–336.
20. Meulenbelt I, Bijkerk C, de Wildt SC, *et al*: **Investigation of the association of the CRTM and CRTL1 genes with radiographically evident osteoarthritis in subjects from the Rotterdam study.** *Arthritis Rheum* 1997, **40**:1760–1765.
21. Meulenbelt I, Bijkerk C, Miedema HS, *et al*: **A genetic association study of the IGF-1 gene and radiological osteoarthritis in a population-based cohort study (the Rotterdam study).** *Ann Rheum Dis* 1998, **57**:371–374.
22. Horton Jr WE, Lethbridge-Cejku M, Hochberg MC, *et al*: **An association between an aggrecan polymorphic allele and bilateral hand osteoarthritis in elderly white men; data from the Baltimore Longitudinal Study of Aging (BLSA).** *Osteoarthritis Cartilage* 1998, **6**:245–251.
23. Loughlin J, Irven C, Ferguson C, Sykes B: **Sibling pair analysis shows no linkage of generalized osteoarthritis to the loci encoding type II collagen, cartilage link protein or cartilage matrix protein.** *Br J Rheumatol* 1994, **33**:1103–1106.
24. Chapman K, Mustafa Z, Irven C, *et al*: **Osteoarthritis-susceptibility locus on chromosome 11 q, detected by linkage.** *Am J Hum Genet* 1999, **65**:167–174.
25. Leppävuori J, Kujala U, Kinnunen J, *et al*: **Genome scan for predisposing loci for distal interphalangeal joint osteoarthritis: evidence for a locus on 2q.** *Am J Hum Genet* 1999, **65**:1060–1067.
26. Loughlin J, Mustafa Z, Irven C, *et al*: **Stratification analysis of an osteoarthritis genome screen suggestive of linkage to chromosomes 4, 6, and 16.** *Am J Hum Genet* 1999, **65**:1795–1798.
27. Felson DT: **Epidemiology of osteoarthritis.** In *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:13–22.
28. McAlindon T, Zhang Y, Hanna M, *et al*: **Are risk factors for patellofemoral and tibiofemoral knee osteoarthritis different?** *J Rheumatol* 1996, **23**:332–337.
29. Felson DT, Zhang Y, Hannan MT, *et al*: **Risk factors for incident radiographic knee osteoarthritis in the elderly.** *Arthritis Rheum* 1997, **40**:728–733.
30. Hart DJ, Doyle DV, Spector TD: **Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women. The Chingford study.** *Arthritis Rheum* 1999, **42**:17–24.
31. Lohmander LS, Roos H: **Knee ligament injury, surgery and osteoarthrosis. Truth or consequences?** *Acta Orthop Scand* 1994, **65**:605–609.
32. Roos H, Laurén M, Adalberth T, *et al*: **Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls.** *Arthritis Rheum* 1998, **41**:687–693.
33. Spector TD, Dacre JE, Harris PA, Huskisson EC: **Radiological progression of osteoarthritis: an 11 year follow up study of the knee.** *Ann Rheum Dis* 1992, **51**:1107–1110.
34. Dieppe PA, Cushnaghan J, Shepstone L: **The Bristol 'OA500' Study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint.** *Osteoarthritis Cartilage* 1997, **5**:87–97.
35. Dougados M, Gueguen A, Nguyen M, *et al*: **Longitudinal radiologic evaluation of osteoarthritis of the knee.** *J Rheumatol* 1992, **19**:378–384.
36. Dougados M, Gueguen A, Nguyen M, *et al*: **Radiological progression of hip osteoarthritis: definition, risk factors and correlations with clinical status.** *Ann Rheum Dis* 1996, **55**:356–362.
37. O'Reilly S, Doherty M: **Signs, symptoms, and laboratory tests.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:197–217.
38. Heinegård D, Bayliss M, Lorenzo P: **Biochemistry and metabolism of normal and osteoarthritic cartilage.** In: *Osteoarthritis*. Edited by Brandt KD, Doheretty M, Lohmander LS. Oxford: Oxford University Press, 1998:74–84.
39. Matyas JR, Ehlers PF, Huang D, Adams ME: **The early molecular natural history of experimental osteoarthritis.** *Arthritis Rheum* 1999, **42**:993–1002.
40. van den Berg WB, van der Kraan PM, van Beuningen HM: **Synovial mediators of cartilage damage and repair in osteoarthritis.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:157–167.
41. Amin AR, Attur M, Abramson SB: **Nitric oxide synthase and cyclooxygenases: distribution, regulation and intervention in arthritis.** *Curr Opin Rheum* 1999, **11**:202–209.
42. Amin AR: **Regulation of tumor necrosis factor-alpha and tumor necrosis factor converting enzyme in human osteoarthritis.** *Osteoarthritis Cartilage* 1999, **7**:392–394.
43. Grodzinsky AJ, Kim Y-J, Buschmann MD, *et al*: **Response of the chondrocyte to mechanical stimuli.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:123–136.
44. Lark MW, Bayne EK, Flanagan J, *et al*: **Aggrecan degradation in human cartilage. Evidence for both matrix metalloproteinase and aggrecanase activity in normal, osteoarthritic, and rheumatoid joints.** *J Clin Invest* 1997, **100**:93–106.
45. Sandy JD, Lark MW: **Proteolytic degradation of normal and osteoarthritic cartilage matrix.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander SL. Oxford: Oxford University Press, 1998:84–93.
46. Lark MW, Bayne EK, Lohmander LS: **Role of stromelysin-1 in cartilage metabolism.** In *Metalloproteinases as Targets for Anti-inflammatory Drugs*. Edited by Bradshaw D, Nixon JS, Bottomley K. Basel: Birkhäuser Verlag, 1999:59–83.
47. Tortorella MD, Burn TC, Pratta MA, *et al*: **Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins.** *Science* 1999, **284**:1664–1666.
48. Rivest C, Liang M: **Evaluating outcome in osteoarthrtis for research and clinical practise.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:403–414.
49. Hart DJ, Spector TD: **Radiographic grading systems.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:450–458.
50. Buckland-Wright JC: **Quantitation of radiographic changes.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:459–472.
51. Peterfy CG: **Magnetic resonance imaging.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:473–494.
52. Lohmander LS, Felson DT: **Defining and validating the clinical role of molecular markers in osteoarthritis.** In: *Osteoarthritis*. Edited by Brandt KD, Doherty M, Lohmander LS. Oxford: Oxford University Press, 1998:519–530.
53. Dieppe P, Chard J, Faulkner A, Lohmander S: **Osteoarthritis.** In: *Clinical Evidence*, vol 2. Edited by Godlee F. London: BMJ Publishing Group, 1999:437–447.
54. Dieppe P: **Osteoarthritis: time to shift the paradigm.** *Br Med J* 1999, **318**:1299–1230.

55. Tanzi RE: **A genetic dichotomy model for the inheritance of Alzheimer's disease and common age-related disorders.** *J Clin Res* 1999, **104**:1175–1179.
56. Velculescu VE, Madden SL, Zhang L, *et al*: **Analysis of human transcriptomes.** *Nature Genet* 1999, **23**:387–388.

Authors affiliation: Department of Orthopedics, University Hospital, Lund, Sweden

Correspondence: L Stefan Lohmander, Department of Orthopedics, University Hospital, SE-22185 Lund, Sweden. Tel: +46 46 171503; fax: +46 46 130732; e-mail: Stefan.Lohmander@ort.lu.se