Takeda, H., Nakagawa, T., Nakamura, K., Engebretsen, L. (2011). Prevention and management of knee osteoarthritis and knee cartilage injury in sports. *British Journal of Sports Medicine, 45*, 304-309

Prevention and management of knee osteoarthritis and knee cartilage injury in sports

Hideki Takeda, M.D., [1, 2] Takumi Nakagawa, M.D., Ph.D.,[2]
Kozo Nakamura, M.D., Ph.D., [2] Lars Engebretsen, M.D., Ph.D.[1]
[1]Oslo Sports Trauma Research Center, Oslo, Norway
[2]Department of Orthopaedic Surgery, Faculty of Medicine,
The University of Tokyo, Tokyo, Japan

Key words : knee, osteoarthritis, sports, prevention, injury, risk factor

Abstract

Articular cartilage defects in the knee of young or active individuals remain a problem in orthopaedic practice. These defects have limited ability to heal and may progress to osteoarthritis (OA). The prevalence of knee OA among athletes is higher than the non-athletic population. The clinical symptoms of OA are joint pain, limitation of range of motion, and joint stiffness. The diagnosis of OA is confirmed by the symptoms of the patient and the radiological findings (narrowing joint space, osteophyte formation, and subchondral sclerosis). However, there is no strong correlation between the symptoms and the radiographic findings.

The etiology of knee OA is multifactorial. Excessive musculoskeletal loading (at work or in sports), high body mass index, previous knee injury, female gender and muscle weakness are well known risk factors. The high level athlete who has sustained a major knee injury has a high incidence of knee OA. Cartilage injuries are frequently observed in young and middle aged active athletes. Often times this injury precedes OA.

Reducing risk factors can decrease the prevalence of knee OA. The prevention of the knee injury, especially anterior cruciate ligament (ACL) and meniscus injury in sports is important to reduce and avoid progression of the knee OA.

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disease and is responsible for decreasing the quality of life among young, active athletes as well as elderly people.[1] The number of people who are affected by OA is increasing due to the increasing age of the population. Obesity, excessive stress to the knee (at work or in sports), previous knee injury, and muscle weakness around knee are known as risk factors.[2-5] In analyzing preventive possibilities, these risk factors are very important.

The aim of this review is to evaluate the prevalence of knee OA and the relationship between sports activity and OA, and furthermore to summarize the prevention and treatment of the knee OA and cartilage injury in sports, in order to reduce the increasing impact of knee OA.

Prevalence of the knee OA in sports

The prevalence of knee OA increases with age.[1] Symptomatic knee OA occurs in 10-38% aged 60 years or older.[6-8] This number is increasing due to the aging of the population. In professional and recreational athletes, prevalence of knee OA depends on the intensity, frequency, level, sports event (Table 1).

Table 1 The prevalence of knee OA in sports

Author	Year	Subject	Number	Mean age	Prevalence of the knee OA
Roos H [9]	1994	Fomer soccer players	286	55	15.5% (elite level) 4.2% (non-elite) 1.6% (control)
Kujala UM[10]	1995	Former top-level athlete	117	45-68	3% (shooter) 29% (soccer) 31% (weight lifter) 14% (runner)
Turner AP[11]	2000	Former professional football players	284	56.1	29% (right knee) 22% (left knee)
Drawer S[12]	2001	Retired professional Soccer players	185	47.6	19% (right knee) 21% (left knee)
Chakravarty EF[13]	2008	Long distance runner	45	76	20%

The prevalence of knee OA among former soccer players is 19-29%, long distance runners 14-20%, and weight lifters 31%.[9-13]. There are some limitations in these studies. Previous studies which showed the relationship between the sport event and the prevalence of knee OA have various definition and criterion of OA, the selection of athlete and the method of analysis.

Definition of knee OA

OA is a group of diseases where the homeostasis of articular cartilage chondrocytes, extracellular matrix and subchondral bone is damaged mechanically and biologically.[14] Although OA may be initiated by multiple factors, including genetic, metabolic, and traumatic, they involve all of the tissues of the joint.[14] OA includes morphologic, biochemical, molecular, and biomechanical changes of both cells and matrix which leads to softening, fibrillation, and ulceration, loss of articular cartilage, sclerosis and eburnation of subchondral bone, osteophytes, and subchondral cysts.[14] Clinical OA is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation. Most physicians diagnose knee OA not only by the symptoms, but by the radiological findings. The usual radiographs are read according to the Kellgren and Lawrence (K&L) classification: grade 0: no changes, grade 1: doubtful narrowing of the joint space and possible osteophytic lipping, grade 2: definite osteophytes and possible narrowing of the joint space, grade 3: moderate multiple osteophytes, definite narrowing of the joint space, and some sclerosis, and possible deformity of the bone ends, grade 4: large osteophytes, marked narrowing of the joint space, severe sclerosis and

definite deformity of the bone ends. Conventionally, OA has been defined as starting at K-L Grade ≥2. [15]

It is important to be aware of the considerable discrepancy between symptoms and radiological findings in OA. Fifteen to eighty one percent of patients with radiographic findings have knee pain in a recent systematic review.[16] On the other hand, patients who have early painful OA might not necessarily have radiographic changes.

Post trauma knee OA in sports

Injuries such as knee ligament tears, meniscal injuries and fractures involving articular surfaces have been shown as strong risk factors for knee OA.[3, 10, 17-19] According to Kujala et al., the risk of knee OA is increased almost 5 times in male former top-level athletes with previous knee injuries (Odds ratio 4.73).[10] Some studies reported that articular surface incongruities greater than 3mm increased local contact stress.[20, 21] Consequently, precise reduction and fracture fixation is needed to avoid knee OA after articular surface fracture. Meniscus injury is a risk factor of knee OA.[3, 18, 22] Table 2 shows the prevalence of radiologic knee OA after meniscectomy with long time follow-up. The mechanical load sharing function is damaged by injured or resected meniscus.[23] The relationship between tear characteristics and the dagree of progression knee OA is controversial.[24-27] Some papers reported that preoperative participation in high level sport is a risk factor for developing radiologic knee OA.[24, 28, 29] The anterior cruciate ligament (ACL) injury is well known as a risk factor of knee OA with or without reconstruction (Table 3).[30-34] Gillquist et al. reported that isolated meniscus tear and subsequent repair, or

ruptures of the ACL seemed to increase the OA risk tenfold compared with an age-matched, uninjured population.[35] In addition, Øiestad et al. showed that the most frequent risk factor for development of knee OA in an ACL injured athlete was meniscal injury. The precalence of knee OA with combination ACL and meniscus injury was much higher than that with isolated ACL injury.[36] Early diagnosis and effective treatment and ensuring complete rehabilitation after ACL and meniscus injury should decrease the risk for OA among sports participants.

Table 2 meniscus injury as a risk factor for knee OA

Author	Year	Number	Follow-up period	Prevalence radiologic knee OA
Jorgensen U[37]	1987	147	4.5 and 14.5 years	12% OA change (4.5 years follow up) 42% OA change (14.5 years follow up)
Maletius W[38]	1996	40	12-15 years	55% OA change
Burks RT[39]	1997	181	10-15 years	62% OA change (more than KL grade 2) with isolated ACL injury 80% OA change (more than KL grade 2) with combined ACL injury
McNicholas MJ[40]	2000	53	30 years	36% OA change
Chatain F[29]	2000	317	10- 15 years	31.2% OA change (medial meniscectomy)
Bonneux I[41]	2002	29	8±1.5 years	43% OA change
Chatain F[24]	2003	471	11 years	21.5% OA change (medial meniscectomy) 37.5% OA change (lateral meniscectomy)
Englund M[42]	2003	155	16± 1years	43% OA change
Englund M[26]	2004	317	18±2 years	27% OA change
Englund M[43]	2004	170	20±2 years	62% OA change

Table 3 ACL injury as a risk factor for knee OA

Author	Year	Background	Number	Study method	Prevalence knee OA
Neyret PH[30]	1993	Non specific sports	93	Cohort 20-35 years follow up	86% OA with untreated ACL injury
von Porat A[31]	2004	Male soccer player	205	Cohort 14 years follow up	78% radiologic OA change (41% more than KL-grade2)
Nebelung W[32]	2005	High level athlete	19	Cohort 35 year follow up	42% TKA with untreated ACL injury
Ait Si Selmi T[33]	2006	Non specific sports	103	Cohort 17 years follow up	14-26% OA with reconstructed ACL (37% with reconstructed ACL and menisectomy)
Øiestad BE[34]	2010	Non specific sports	181	Cohort 10-15 years follow up	62% radiologic OA (more than KL grade 2) with isolated ACL injury 80% radiologic OA (more than KL grade 2) with combined ACL injury

Are the sports themselves causing OA?

Epidemiologic studies have showed that participation in some competitive sports increases the risk for OA.[4, 44, 45] Moderate exercise has low risk of leading to OA. Furthermore, there is evidence that appropriate exercise reduces disability in the knee.[46] Sports activities including high-intensity and direct joint impact as a result of contact with other participants appeared to increase the risk for OA.[47] Repetitive impact and twisting loads to the knee were also associated with joint degeneration.[5, 10, 48, 49] To avoid knee OA, participant should pay attention to individual risk factors, frequency and intensity of sports activity.

The cartilage injury in athletes

In a study of 993 consecutive arthroscopies in patients with knee pain from Norway, articular cartilage changes were noted in 66% of the knees and isolated, localized cartilage lesions in about 20% of the cases.[50] Full thickness cartilage lesions were found in 11% of the knees. Sports participation was the most commonly reported activity (49%). Most of the patients with localized cartilage lesions were in the younger age groups (median age: 30 years). The most serious cartilage injuries ICRS grade III and IV were commonly located at the medial femoral condyle followed by the patella. A single full-thickness area of more than 2 cm^2 was observed in 6% of all knees, and half of these patients had a cartilage lesion as their only pathology. Fifty percent of these larger lesions (grade III-IV and >2 cm^2) were localized in the medial femoral condyle and 13% in the femoral trochlea.

Cartilage treatment should be aimed at restoring the normal knee function

by regeneration of hyaline cartilage in the defect, and to achieve a complete integration of the new cartilage to the surrounding cartilage and underlying bone. Recent years have seen several new surgical procedures emerge with the aim to improve function and to create normal cartilage. Unfortunately, clinical studies have been limited by methodological weaknesses. Over the last 10 years, marrow-stimulating procedures such as the microfracture method have been widely used and so far no other procedure has surpassed the microfracture results. The main developmental research has occurred in autologous chondrocyte implantation (ACI) which was first described in 1994.[51] Newer techniques combining scaffolds, cells and growth factors have since been developed [52-57].

Ninety percent of rotational injuries to the knee include the so called bone bruise lesion.[58] Follow-up MRI studies of patients with bone bruises suggest that this may lead to degeneration of the cartilage and early arthritis.[58] In addition, it has been shown that isolated cartilage injuries may lead to degeneration of the adjacent cartilage.[59] These changes may be caused by the abnormally high stresses acting on the rim of the defect. The cartilage surface opposing an isolated cartilage injury often show fibrillation caused by mechanical irritation.[60] Thus, it is suggested that rotational injury to the knee with a bone bruise and subsequent cartilage changes may progress into degenerative arthritis. Moreover, the presence of concomitant injuries (for example, ACL injury or meniscus injury) and malalignment of the lower extremity influences management of these lesions. [48, 61-63] Below is a brief description of the most used techniques for cartilage treatment.

a. Microfracture

Microfracture as a minimally invasive and simple procedure and is considered the first choice of treatment for the patients with previously untreated cartilage defects. This technique has the goal of recruiting pluripotential stem cells from the marrow by penetrating the subchondral bone. The preferable cartilage lesion for this method is relatively small size (1-2cm^2). Only two controlled, randomized clinical studies exist.[64, 65] Knutsen et al. have found good pain relief after 2 years of follow-up in 70-80% of the patients, whereas Gudas et al. found superiority of the osteochondral autologous transplantation over microfracture at 1, 2 and 3 years time-points.[64, 65] Further, the Norwegian study comparing ACIs with microfracture did not see deterioration in the clinical results even 5 years after surgery.[66] There are few studies investigating the rate of return to sports after microfracture.[65, 67-70] Steadman reported that 76% of NFL players returned to play 4.6 more seasons after microfracture.[67] In contrast, Namdari et al. showed that only 58% of NBA players after microfracture were able to return to play at least 1 more season.[68] There is an obvious need for studies with more participants.

b. Autologous chondrocyte implantation (ACI)

Autologous chondrocytes for cell transplantation to regenerate cartilage has been widely used.[51, 71-73] The procedure involves harvesting of 2-300 mg of cartilage through an arthroscopic procedure, followed 2-4 weeks later by an arthrotomy, where the cells are injected under a cover of periosteum or a synthetic membrane. So far the results of four controlled studies have been published. Bentley et al. showed that after 19 months, 88% of the patients in the cell group versus 69% in the mosaic group had good to excellent results

based on two non-validated scoring systems.[74] Horas et al. found no differences between cells and mosaicplasty after two years.[75] Dozin et al. also concluded that ACI and mosaicplasty were clinically equivalent and similar in performance.[76] The Norwegian study[64] found no difference between cell transplantation and microfractures—both leading to improvement in more than 75% of the patients after two years.[64] There was no significant difference in macroscopic or histological results between the two treatment groups and no association between the histological findings and the clinical outcome at the two-year time-point. Furthermore, the Norwegian study comparing ACIs with microfracture, did not see a deterioration in the clinical results even 5 years after surgery.[66] Hypertrophy of tissue seemed to be the major cause for re-operations after ACI.[77] Recently, Saris et al published 3 year followup of optimized chondocyte implantation resulting in improved clinical outcomes compared to microfracture.[78] Kreuz et al. showed the rate of return to preinjury level of sports after ACI among regular or competitive sports athletes was 94 % at 18 months follow up.[79] The improvement will peak at approximately 2 years, and it does not seem to deteriorate up to 8 years. At the moment the procedure is reserved for patients with large defects on the weightbearing surface of the knee joint. The defects should not be deeper than approximately 5 millimeters without being bone grafted. ACI may be preferred as a second-line treatment for large defects. Recently microfracture was found to have less favorable results in treating patellofemoral lesions and ACI may be a better option for trochlear defects.[80]

c. Matrix guided autologous chondrocyte implantation (MACI)

MACI is invented to improve upon disadvantages of ACI (hypertrophy of the

graft, the uneven distribution of chondrocytes within the defect and the potential for cell leakage). In MACI, cultured chondrocyte is cultured and implanted in scaffold. However, so far the clinical and histological results have not been reported to be better than conventional ACI.[81]

d. Mosaicplasty and osteochondral autologous grafts

An alternative to biological regeneration of a defect is to replace it with a substitute. Several orthopedic companies have produced coring drills, which will harvest plug from areas with relatively less weightbearing such as the intercondylar notch or the most lateral part of the femoral condyle. The plugs are then placed in the defect in predrilled cylinders. The clinical data was first published by Hangody and Bobic.[82, 83] And the results matched those after chondrocyte transplantation by Brittberg et al.[51] The recent study by Bentley et al. showed less encouraging results for this technique, while the Horas study and the Dozin study reported more optimistic results.[74-76] Furthermore, the study by Gudas et al. has shown significant superiority of this technique over microfracture procedures, and showed that the rate of return to sports after mosaicplasty was 93 % at an average of 6.5 months.[65] There is an obvious need for longer follow-up studies. The use of this technique is limited only by the size of the defect due to the necessity of harvesting from relatively less weight bearing areas. Recently synthetic plugs have been developed for clinical use as a substitute for autologous graft (True-Fit, Smith & Nephew).[84-86] However no long term results have been published.

e. Mesenchymal stem cell (MSC) transplantation

MSC transplantation has been introduced to repair the cartilage lesions avoiding the disadvantage of other methods. MSCs retain both high

proliferative potential and multipotentiality, including chondrogenic differentiation potential, and a number of animal studies with this method were reported.[87] The use of MSCs for cartilage repair is still at the early stage. More clinical studies are needed.

Treatment of knee OA in athletes

Surgical treatment

Patients with knee OA who are not obtaining adequate pain relief and functional improvement from a combination of rehabilitation and pharmacological treatment are considered for surgical treatments. There is agreement that arthroscopi debridement is not an efficient procedure in OA patients.[88] For the young and active athletes with symptomatic medial unicompartmental knee OA, high tibial osteotomy (HTO) may avoid progression of disease. The HTO is can be done with an open-wedge osteotomy or lateral closing-wedge osteotomy. The medial tibial osteotomy is a popular technique and avoids detachment of the tibials anterior muscle, the risk of peroneal nerve palsy and loss of correction to the lateral tibial osteotomy.[89] For the older athletes with knee OA, unicompartmental or total knee arthroplasty may be considered to improve quality of life as well as some sports activity. Even though HTO and knee arthroplasty are common, there is limited literature reporting on the relationship sports activity and knee surgery. Only 2 studies that reported clinical results involving return to sports and heavy works after HTO were found. They showed that 75-91 % of patients after HTO were engaged in sports and recreational activities and re-gained the frequency and duration of sports

activities.[90, 91] In the older patient group, several studies reported that more than 90 % of the patients after UKA, and more than 60 % of the patients after TKA returned to the same level of sports activity as before surgery.[92-96] Further studies focusing on the appropriate level of sports activity after knee intervention and the prevention of the implant problem (prosthetic wear out, loosening) among athletes are clearly needed.

Prevention of the knee OA in sports

As the number of the people who suffer OA disease is increasing, prevention of OA is important and necessary. The OA disease has three strong risk factors (excessive musculoskeletal loading, high body mass index, and previous knee injury) where prevention may work. According to Hochberg MC., avoiding squatting and kneeling and carrying heavy loads during work have been associated with a reduction of 15–30% in the prevalence of OA in men.[97] Another study showed a significant exposure-response relationship between symptomatic knee OA and squatting and kneeling.[98, 99] Overweight is a risk factor for knee OA. Weight reduction reduces not only symptom and progression of OA, but also risk from acquiring OA.[100, 101] The osteoarthritis research society international (OARSI) group strongly recommends that the patients with OA lose weight and maintain weight at a lower level in overweight patients[102]. Maintaining the body mass index (BMI) at 25 kg/m^2 or below would reduce OA of the population by 27–53%.[97, 98] As mentioned, knee injuries such as knee ligament tears, meniscal injuries and fractures involving articular surfaces is a strong risk factor for knee OA. Recently, prevention programs of sports injury, especially in ACL injury have shown encouraging results. Norwegian studies showed that

prevention of ACL injuries was possible with the use of neuromuscular training programs.[103-105] According to Felson[98] et al. prevention of joint injuries would give an additional 14% to 25% reduction in OA prevalence.

Summary: Ligament, meniscal and cartilage injuries are common in sports. Unfortunately, at the present time our treatment being surgical or rehabilitation does not seem to avoid the development of OA in the knee. Much is happening in research on surgical as well as rehabilitation procedures in this field. Clearly, a higher emphasize on prevention is necessary.

References

1. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ* 2003;81(9):646-56.
2. Toivanen AT, Heliovaara M, Impivaara O, et al. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis--a population-based study with a follow-up of 22 years. *Rheumatology (Oxford)* 2010;49(2):308-14.
3. Cooper C, Snow S, McAlindon TE, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis Rheum* 2000;43(5):995-1000.
4. Thelin N, Holmberg S, Thelin A. Knee injuries account for the sports-related increased risk of knee osteoarthritis. *Scand J Med Sci Sports* 2006;16(5):329-33.
5. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med* 2000;133(8):635-46.
6. Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. *Arthritis Rheum* 1987;30(8):914-8.
7. Felson DT. An update on the pathogenesis and epidemiology of osteoarthritis. *Radiol Clin North Am* 2004;42(1):1-9, v.
8. Dillon CF, Rasch EK, Gu Q, et al. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *J Rheumatol* 2006;33(11):2271-9.
9. Roos H, Lindberg H, Gardsell P, et al. The prevalence of gonarthrosis and its relation to meniscectomy in former soccer players. *Am J Sports Med* 1994;22(2):219-22.

10. Kujala UM, Kettunen J, Paananen H, et al. Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. *Arthritis Rheum* 1995;38(4):539-46.
11. Turner AP, Barlow JH, Heathcote-Elliott C. Long term health impact of playing professional football in the United Kingdom. *Br J Sports Med* 2000;34(5):332-6.
12. Drawer S, Fuller CW. Propensity for osteoarthritis and lower limb joint pain in retired professional soccer players. *Br J Sports Med* 2001;35(6):402-8.
13. Chakravarty EF, Hubert HB, Lingala VB, et al. Long distance running and knee osteoarthritis. A prospective study. *Am J Prev Med* 2008;35(2):133-8.
14. Kuettner KE, Goldberg VM. Introduction. In: Kuettner KE, Goldberg VM, editors. *Osteoarthritis disorders*. Rosemont: American Academy of Orthpaedic Surgeons, 1995:xxi-xxv.
15. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16(4):494-502.
16. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord* 2008;9:116.
17. Rall KL, McElroy GL, Keats TE. A Study of Long Term Effects of Football Injury to the Knee. *Mo Med* 1964;61:435-8.
18. Gelber AC, Hochberg MC, Mead LA, et al. Joint injury in young adults and risk for subsequent knee and hip osteoarthritis. *Ann Intern Med* 2000;133(5):321-8.
19. Sutton AJ, Muir KR, Mockett S, et al. A case-control study to investigate the relation between low and moderate levels of physical activity and osteoarthritis of the knee using data collected as part of the Allied Dunbar National Fitness Survey. *Ann Rheum Dis* 2001;60(8):756-64.
20. Brown TD, Anderson DD, Nepola JV, et al. Contact stress aberrations following imprecise reduction of simple tibial plateau fractures. *J Orthop Res* 1988;6(6):851-62.
21. Huber-Betzer H, Brown TD, Mattheck C. Some effects of global joint morphology on local stress aberrations near imprecisely reduced intra-articular fractures. *J Biomech* 1990;23(8):811-22.
22. Englund M, Guermazi A, Roemer FW, et al. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The Multicenter Osteoarthritis Study. *Arthritis Rheum* 2009;60(3):831-9.
23. Aagaard H, Verdonk R. Function of the normal meniscus and consequences of meniscal resection. *Scand J Med Sci Sports* 1999;9(3):134-40.
24. Chatain F, Adeleine P, Chambat P, et al. A comparative study of medial versus lateral arthroscopic partial meniscectomy on stable knees: 10-year minimum follow-up. *Arthroscopy* 2003;19(8):842-9.
25. Bolano LE, Grana WA. Isolated arthroscopic partial meniscectomy. Functional radiographic evaluation at five years. *Am J Sports Med* 1993;21(3):432-7.
26. Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to

twenty-two years after meniscectomy. *Arthritis Rheum* 2004;50(9):2811-9.
27. Hede A, Larsen E, Sandberg H. The long term outcome of open total and partial meniscectomy related to the quantity and site of the meniscus removed. *Int Orthop* 1992;16(2):122-5.
28. Stehling C, Lane NE, Nevitt MC, et al. Subjects with higher physical activity levels have more severe focal knee lesions diagnosed with 3T MRI: analysis of a non-symptomatic cohort of the osteoarthritis initiative. *Osteoarthritis Cartilage* 2010;18(6):776-86.
29. Chatain F, Robinson AH, Adeleine P, et al. The natural history of the knee following arthroscopic medial meniscectomy. *Knee Surg Sports Traumatol Arthrosc* 2001;9(1):15-8.
30. Neyret P, Donell ST, Dejour H. Results of partial meniscectomy related to the state of the anterior cruciate ligament. Review at 20 to 35 years. *J Bone Joint Surg Br* 1993;75(1):36-40.
31. von Porat A, Roos EM, Roos H. High prevalence of osteoarthritis 14 years after an anterior cruciate ligament tear in male soccer players: a study of radiographic and patient relevant outcomes. *Ann Rheum Dis* 2004;63(3):269-73.
32. Nebelung W, Wuschech H. Thirty-five years of follow-up of anterior cruciate ligament-deficient knees in high-level athletes. *Arthroscopy* 2005;21(6):696-702.
33. Ait Si Selmi T, Fithian D, Neyret P. The evolution of osteoarthritis in 103 patients with ACL reconstruction at 17 years follow-up. *Knee* 2006;13(5):353-8.
34. Oiestad BE, Holm I, Aune AK, et al. Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction: a prospective study with 10 to 15 years of follow-up. *Am J Sports Med* 2010;38(11):2201-10.
35. Gillquist J, Messner K. Anterior cruciate ligament reconstruction and the long-term incidence of gonarthrosis. *Sports Med* 1999;27(3):143-56.
36. Oiestad BE, Engebretsen L, Storheim K, et al. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. *Am J Sports Med* 2009;37(7):1434-43.
37. Jorgensen U, Sonne-Holm S, Lauridsen F, et al. Long-term follow-up of meniscectomy in athletes. A prospective longitudinal study. *J Bone Joint Surg Br* 1987;69(1):80-3.
38. Maletius W, Messner K. Chondral damage and age depress the long-term prognosis after partial meniscectomy. A 12- to 15-year follow-up study. *Knee Surg Sports Traumatol Arthrosc* 1996;3(4):211-4.
39. Burks RT, Metcalf MH, Metcalf RW. Fifteen-year follow-up of arthroscopic partial meniscectomy. *Arthroscopy* 1997;13(6):673-9.
40. McNicholas MJ, Rowley DI, McGurty D, et al. Total meniscectomy in adolescence. A thirty-year follow-up. *J Bone Joint Surg Br* 2000;82(2):217-21.
41. Bonneux I, Vandekerckhove B. Arthroscopic partial lateral meniscectomy long-term results in athletes. *Acta Orthop Belg* 2002;68(4):356-61.
42. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. *Arthritis Rheum* 2003;48(8):2178-87.

43. Englund M, Paradowski PT, Lohmander LS. Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. *Arthritis Rheum* 2004;50(2):469-75.
44. Spector TD, Harris PA, Hart DJ, et al. Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. *Arthritis Rheum* 1996;39(6):988-95.
45. Sandmark H, Vingard E. Sports and risk for severe osteoarthrosis of the knee. *Scand J Med Sci Sports* 1999;9(5):279-84.
46. Roddy E, Zhang W, Doherty M, et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee--the MOVE consensus. *Rheumatology (Oxford)* 2005;44(1):67-73.
47. Deacon A, Bennell K, Kiss ZS, et al. Osteoarthritis of the knee in retired, elite Australian Rules footballers. *Med J Aust* 1997;166(4):187-90.
48. Buckwalter JA, Lane NE. Athletics and osteoarthritis. *Am J Sports Med* 1997;25(6):873-81.
49. Buckwalter JA, Lane NE. Does participation in sports cause osteoarthritis? *Iowa Orthop J* 1997;17:80-9.
50. Aroen A, Loken S, Heir S, et al. Articular cartilage lesions in 993 consecutive knee arthroscopies. *Am J Sports Med* 2004;32(1):211-5.
51. Brittberg M, Lindahl A, Nilsson A, et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 1994;331(14):889-95.
52. Krishnan SP, Skinner JA, Carrington RW, et al. Collagen-covered autologous chondrocyte implantation for osteochondritis dissecans of the knee: two- to seven-year results. *J Bone Joint Surg Br* 2006;88(2):203-5.
53. Bartlett W, Skinner JA, Gooding CR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. *J Bone Joint Surg Br* 2005;87(5):640-5.
54. Nehrer S, Domayer S, Dorotka R, et al. Three-year clinical outcome after chondrocyte transplantation using a hyaluronan matrix for cartilage repair. *Eur J Radiol* 2006;57(1):3-8.
55. Behrens P, Bitter T, Kurz B, et al. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)--5-year follow-up. *Knee* 2006;13(3):194-202.
56. Steinwachs M, Kreuz PC. Autologous chondrocyte implantation in chondral defects of the knee with a type I/III collagen membrane: a prospective study with a 3-year follow-up. *Arthroscopy* 2007;23(4):381-7.
57. van den Berg WB, van der Kraan PM, Scharstuhl A, et al. Growth factors and cartilage repair. *Clin Orthop Relat Res* 2001(391 Suppl):S244-50.
58. Engebretsen L, Arendt E, Fritts HM. Osteochondral lesions and cruciate ligament injuries. MRI in 18 knees. *Acta Orthop Scand* 1993;64(4):434-6.
59. Wei X, Messner K. Maturation-dependent durability of spontaneous cartilage repair in

rabbit knee joint. *J Biomed Mater Res* 1999;46(4):539-48.
60. Twyman RS, Desai K, Aichroth PM. Osteochondritis dissecans of the knee. A long-term study. *J Bone Joint Surg Br* 1991;73(3):461-4.
61. Sharma L, Hurwitz DE, Thonar EJ, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. *Arthritis Rheum* 1998;41(7):1233-40.
62. Honkonen SE. Degenerative arthritis after tibial plateau fractures. *J Orthop Trauma* 1995;9(4):273-7.
63. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instr Course Lect* 1998;47:487-504.
64. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J Bone Joint Surg Am* 2004;86-A(3):455-64.
65. Gudas R, Stankevicius E, Monastyreckiene E, et al. Osteochondral autologous transplantation versus microfracture for the treatment of articular cartilage defects in the knee joint in athletes. *Knee Surg Sports Traumatol Arthrosc* 2006;14(9):834-42.
66. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. *J Bone Joint Surg Am* 2007;89(10):2105-12.
67. Steadman JR, Briggs KK, Rodrigo JJ, et al. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy* 2003;19(5):477-84.
68. Namdari S, Baldwin K, Anakwenze O, et al. Results and performance after microfracture in National Basketball Association athletes. *Am J Sports Med* 2009;37(5):943-8.
69. Riyami M, Rolf C. Evaluation of microfracture of traumatic chondral injuries to the knee in professional football and rugby players. *J Orthop Surg Res* 2009;4:13.
70. Gobbi A, Nunag P, Malinowski K. Treatment of full thickness chondral lesions of the knee with microfracture in a group of athletes. *Knee Surg Sports Traumatol Arthrosc* 2005;13(3):213-21.
71. Peterson L, Minas T, Brittberg M, et al. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop Relat Res* 2000(374):212-34.
72. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. *Clin Orthop Relat Res* 2001(391 Suppl):S349-61.
73. Peterson L, Brittberg M, Kiviranta I, et al. Autologous chondrocyte transplantation. Biomechanics and long-term durability. *Am J Sports Med* 2002;30(1):2-12.
74. Bentley G, Biant LC, Carrington RW, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br* 2003;85(2):223-30.
75. Horas U, Pelinkovic D, Herr G, et al. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective,

comparative trial. *J Bone Joint Surg Am* 2003;85-A(2):185-92.
76. Dozin B, Malpeli M, Cancedda R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. *Clin J Sport Med* 2005;15(4):220-6.
77. Muellner T, Knopp A, Ludvigsen TC, et al. Failed autologous chondrocyte implantation. Complete atraumatic graft delamination after two years. *Am J Sports Med* 2001;29(4):516-9.
78. Saris DB, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med* 2009;37 Suppl 1:10S-19S.
79. Kreuz PC, Steinwachs M, Erggelet C, et al. Importance of sports in cartilage regeneration after autologous chondrocyte implantation: a prospective study with a 3-year follow-up. *Am J Sports Med* 2007;35(8):1261-8.
80. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage* 2006;14(11):1119-25.
81. Iwasa J, Engebretsen L, Shima Y, et al. Clinical application of scaffolds for cartilage tissue engineering. *Knee Surg Sports Traumatol Arthrosc* 2009;17(6):561-77.
82. Bobic V. Arthroscopic osteochondral autograft transplantation in anterior cruciate ligament reconstruction: a preliminary clinical study. *Knee Surg Sports Traumatol Arthrosc* 1996;3(4):262-4.
83. Hangody L, Feczko P, Bartha L, et al. Mosaicplasty for the treatment of articular defects of the knee and ankle. *Clin Orthop Relat Res* 2001(391 Suppl):S328-36.
84. Safran MR, Kim H, Zaffagnini S. The use of scaffolds in the management of articular cartilage injury. *J Am Acad Orthop Surg* 2008;16(6):306-11.
85. Williams RJ, Gamradt SC. Articular cartilage repair using a resorbable matrix scaffold. *Instr Course Lect* 2008;57:563-71.
86. Kerker JT, Leo AJ, Sgaglione NA. Cartilage repair: synthetics and scaffolds: basic science, surgical techniques, and clinical outcomes. *Sports Med Arthrosc* 2008;16(4):208-16.
87. Koga H, Engebretsen L, Brinchmann JE, et al. Mesenchymal stem cell-based therapy for cartilage repair: a review. *Knee Surg Sports Traumatol Arthrosc* 2009;17(11):1289-97.
88. Moseley B. Arthroscopic surgery did not provide additional benefit to physical and medical therapy for osteoarthritis of the knee. *J Bone Joint Surg Am* 2009;91(5):1281.
89. Lobenhoffer P, Agneskirchner JD. Improvements in surgical technique of valgus high tibial osteotomy. *Knee Surg Sports Traumatol Arthrosc* 2003;11(3):132-8.
90. Odenbring S, Tjornstrand B, Egund N, et al. Function after tibial osteotomy for medial gonarthrosis below aged 50 years. *Acta Orthop Scand* 1989;60(5):527-31.
91. Salzmann GM, Ahrens P, Naal FD, et al. Sporting activity after high tibial osteotomy for

the treatment of medial compartment knee osteoarthritis. *Am J Sports Med* 2009;37(2):312-8.
92. Bradbury N, Borton D, Spoo G, et al. Participation in sports after total knee replacement. *Am J Sports Med* 1998;26(4):530-5.
93. Fisher N, Agarwal M, Reuben SF, et al. Sporting and physical activity following Oxford medial unicompartmental knee arthroplasty. *Knee* 2006;13(4):296-300.
94. Naal FD, Fischer M, Preuss A, et al. Return to sports and recreational activity after unicompartmental knee arthroplasty. *Am J Sports Med* 2007;35(10):1688-95.
95. Hopper GP, Leach WJ. Participation in sporting activities following knee replacement: total versus unicompartmental. *Knee Surg Sports Traumatol Arthrosc* 2008;16(10):973-9.
96. Walton NP, Jahromi I, Lewis PL, et al. Patient-perceived outcomes and return to sport and work: TKA versus mini-incision unicompartmental knee arthroplasty. *J Knee Surg* 2006;19(2):112-6.
97. Hochberg M. Prevention of lower limb osteoarthritis: data from the Johns Hopkins Precursors Study. In: Hascall VC, Kuettner KE, editors. *The many faces of osteoarthritis*. Basel: Birkhauser, 2002:31-37.
98. Felson DT. Preventing knee and hip osteoarthritis. *Bull Rheum Dis* 1998;47(7):1-4.
99. Felson DT, Hannan MT, Naimark A, et al. Occupational physical demands, knee bending, and knee osteoarthritis: results from the Framingham Study. *J Rheumatol* 1991;18(10):1587-92.
100. Felson DT, Zhang Y, Anthony JM, et al. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Ann Intern Med* 1992;116(7):535-9.
101. Manninen P, Riihimaki H, Heliovaara M, et al. Overweight, gender and knee osteoarthritis. *Int J Obes Relat Metab Disord* 1996;20(6):595-7.
102. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16(2):137-62.
103. Olsen OE, Myklebust G, Engebretsen L, et al. Exercises to prevent lower limb injuries in youth sports: cluster randomised controlled trial. *BMJ* 2005;330(7489):449.
104. Myklebust G, Engebretsen L, Braekken IH, et al. Prevention of anterior cruciate ligament injuries in female team handball players: a prospective intervention study over three seasons. *Clin J Sport Med* 2003;13(2):71-8.
105. Soligard T, Myklebust G, Steffen K, et al. Comprehensive warm-up programme to prevent injuries in young female footballers: cluster randomised controlled trial. *BMJ* 2008;337:a2469.