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CLINICAL REVIEW

Treating articular cartilage injuries of the knee in young people

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Articular chondral and osteochondral injuries of the knee are common in people aged under 35 years, and symptomatic lesions left untreated may lead to chronic pain and disability. Patients with articular chondral injuries often have a poorer function score than those awaiting surgery for other knee disorders, such as osteoarthritis or a ruptured anterior cruciate ligament.[1] Patients with articular cartilage injuries may go on to develop early onset osteoarthritis with long term morbidity and consequent high use of health service resources; successful early treatment of these lesions would probably be cost effective.

Chondral and osteochondral lesions may not be diagnosed or may present late because patients will often give a history of an apparent insignificant trauma and doctors may fail to understand the importance of an effusion in the knee joint, which always indicates joint disease.[2] Radiographs of the knee may be poorly interpreted. This review discusses the diagnosis and management (conservative and surgical) of injuries to the articular cartilage of the knee and draws on published research articles and the authors' own experience.

SUMMARY POINTS

- Articular cartilage injuries of the knee are common in people aged under 35 years
- If symptomatic they can be debilitating and may progress to osteoarthritis
- Early appropriate treatment of symptomatic lesions may prevent the onset of osteoarthritis and is cost effective

Methods

We searched the Cochrane database, PubMed, and Google Scholar up to December 2009. We analysed randomised controlled trials and comparison trials, as well as articles on operative technique and case series.

How are articular chondral injuries of the knee classified?

Long bone articular surfaces are covered with hyaline cartilage. Damage to this hyaline cartilage is known as a chondral injury or, if the underlying bone is also fractured, an osteochondral injury.

Articular cartilage is avascular and aneural, so pain would not be expected. Yet some patients with chondral lesions do present with pain. A widely accepted hypothesis for the presence of this pain is that it is caused by the increased load on the subchondral bone resulting from damage or loss of overlying cartilage.

The problems with articular cartilage are that it has little capacity to repair itself or regenerate intrinsically.[3 w1 w2] Therefore cartilage defects repair by forming scar tissue from the subchondral bone. This scar tissue is deficient in type II collagen and has "abnormal" proteoglycans (which have inferior biomechanical characteristics) and lower load bearing capacity, and its formation will often result in short term recovery. This later surface deterioration may progress to give chronic pain and poor function and may in some cases lead to early onset osteoarthritis.[4 w3 w4]

Who gets articular chondral injuries of the knee?

A regional database study of over 30 000 patients found that 63% of knees that undergo arthroscopy are found to have disease in the articular cartilage[5] and articular chondral lesions are suspected to be the cause of as many as 10% of all knee haemarthroses.[6]

Trauma is the most common aetiology,[6 w5] but other conditions, such as osteochondritis dissecans[7 w6] and chondromalacia patellae (abnormal softening of the patellar articular cartilage),[8 w7] are also accepted as causes of symptomatic painful articular lesions. Isolated articular cartilage injuries secondary to trauma are rare; more often articular cartilage injuries are seen with other traumatic injuries to the knee, such as ligamentous or meniscal damage.[w8]

A recent magnetic resonance imaging study found that after acute trauma the most common injuries to the immature knee were chondral in nature.[9]

Osteochondral lesions are most common in adolescents[w9] as the cartilage has yet to calcify. Traumatic forces are transmitted through the subchondral bone beneath the cartilage, resulting in an osteochondral fracture.

How do you make a diagnosis?

Patients with symptoms present with a painful knee. Pain may be present at rest and is exacerbated by weight bearing exercises. The knee may give way if a longstanding injury results in substantial muscle wasting or there is associated ligamentous instability. Locking is seen if a loose osteochondral fragment impedes articular movement.

The most common findings on examination are tenderness on palpation of the joint line, with pain induced by both passive and active movements. The examiner will see wasting of the quadriceps and feel crepitus on passive

joint movement in a usually stable knee. These clinical findings are not specific to chondral and osteochondral lesions.

The optimal assessment of articular injuries of the knee remains the examination of the knee under anaesthesia followed by arthroscopy; this allows for direct visualisation to establish the size, site, and depth of the chondral lesion and the ligamentous integrity of the knee.

Other diagnostic tools include magnetic resonance imaging, which provides accuracy with high levels of reproducibility.[w10 w11] Delayed, gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC) visualises the glycosaminoglycan content of the cartilage and is useful in diagnosing early osteoarthritis and cartilage health.[w12]

How are injuries of the articular cartilage treated?

Conservative management

Animal studies have shown that continuous passive motion enhances the healing potential of articular cartilage. It has two potential mechanisms of action. Firstly, it enables the movement of synovial fluid, allowing better diffusion of nutrients into damaged cartilage and diffusion out of other materials (such as blood and metabolic waste products). Secondly, it reduces the formation of fibrous scar tissue in the joint; this tends to decrease the range of motion for a joint, which enhances the healing potential of articular cartilage.[w13] Although animal models showed satisfactory results, the healing noted was much less pronounced in lesions greater than 3 mm^2.[10]

What are the indications for surgery?

Little evidence exists for the need to treat asymptomatic defects that are found incidentally. However, there are animal and cadaveric studies suggesting that defects larger than 6 mm will not heal spontaneously.[11 w14]

In general, injuries that are new are given time to settle to see if the chondral lesion will become symptomatic or not. Observational evidence suggests that after the initial acute phase, if pain fails to resolve, surgical treatment gives better outcomes if done sooner rather than later.[12-14]

Treatment of larger and symptomatic lesions is surgical. Interventions that have been investigated and used are arthroscopic debridement, marrow stimulating techniques, autologous chondrocyte transfers and implantation, and allografts.

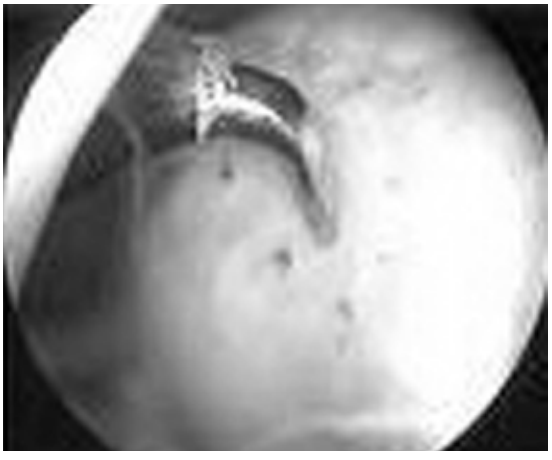

Fig 1 | Arthroscopic microfracture

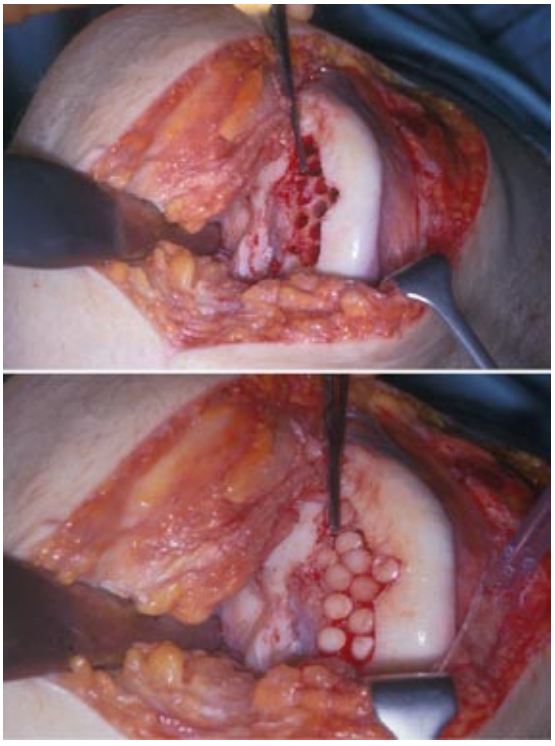

Fig 2 | Defect site before (top) and after (bottom) mosaic plugs were used to fill the defect. Reproduced from Bentley et al[24] with permission of the British Editorial Society of Bone and Joint Surgery

Ideally the aim of surgery is to provide an environment that allows whatever repair tissue is produced (preferably hyaline cartilage) to be integrated with native healthy tissue to provide long term durability and a "normal" knee joint.[w15 w16]

Arthroscopic debridement

Arthroscopic debridement involves removal of fragments of loose cartilage to provide temporary symptomatic relief. Relief is only transient as the washout clears inflammatory debris but does not treat the underlying articular cartilage injury. A randomised controlled study found that painful symptoms usually return within five years and continued chondral deterioration occurs within the affected joint.[15]

Marrow stimulating techniques (reparative)

Abrasion chondroplasty

The aim of abrasion chondroplasty is to induce fibrocartilage growth into the chondral defect by causing a "therapeutic" bleeding, resulting in a clot that forms fibrocartilage. Johnson reviewed the literature and his own case series and found that chondroplasty improved symptoms in the first 12 months postoperatively, although a return to preoperative symptoms was often seen beyond 24 months (this return to previous symptoms, however, was in an older population with established arthritic changes).[w17]

Bone drilling

Bone drilling, first described in 1959 as a method of resurfacing osteoarthritic knees,[w18] is now practised as a technique to stimulate reparative growth of damaged or missing articular cartilage. Holes of 2-2.5 mm diameter are drilled into the subchondral layer of bone in the defect. Drilling results in substantial thermal heat, which has been suggested as causing damage to the subchondral bone, thus impeding healing. This hypothesis, however, has never been proved. Bone drilling is an open arthrotomy procedure and hence has higher morbidity compared with other marrow stimulating techniques that can be performed arthroscopically. Drilling has now largely been superseded by other techniques.

Microfracture

Microfracture (fig 1) involves the perforation of the subchondral bone using a sharp awl. The technique, first described in 1997, is a refined form of bone drilling. The aim is to release pluripotent stem cells from within the subchondral bone along with growth factors and cytokines, thus producing a clot rich in regenerative cells, an ideal environment for fibrocartilage repair.[16 w19] Unlike drilling, microfracture does not produce enough heat to damage subchondral bone and is almost always performed arthroscopically. A randomised controlled study suggested that microfracture produces equivalent results to its more expensive alternatives for as long as five years.[17] However, the technique produces fibrocartilage that does not possess the same properties as the lost hyaline cartilage and that may not have the longevity of hyaline type cartilage.[18 w20] Best results have been shown in slim athletic patients[17 w21 w22] with microfracture of the femoral condyle.[19]

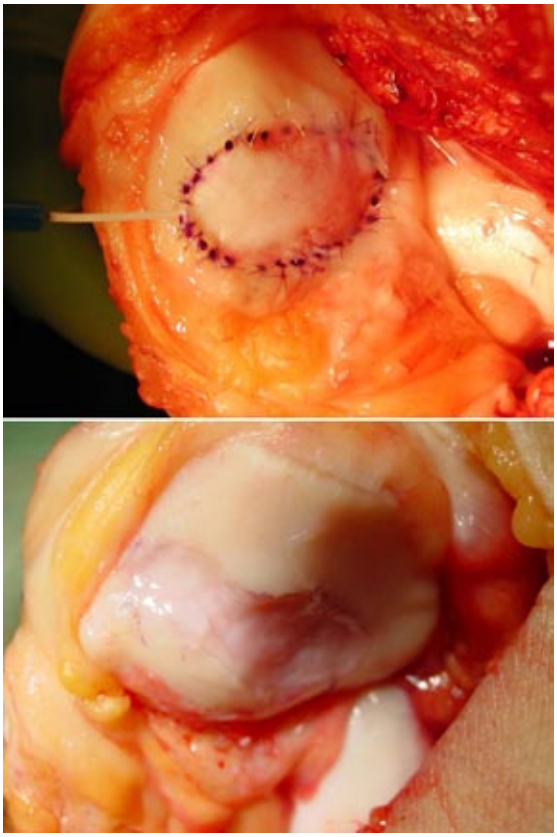

Fig 3 | Top: Narrow cannula in situ injecting cells beneath sutured type I/III collagen membrane. Bottom: Matrix assisted autologous chondrocyte implantation: seeded cells on a type I/III collagen membrane "glued" into position with fibrin glue

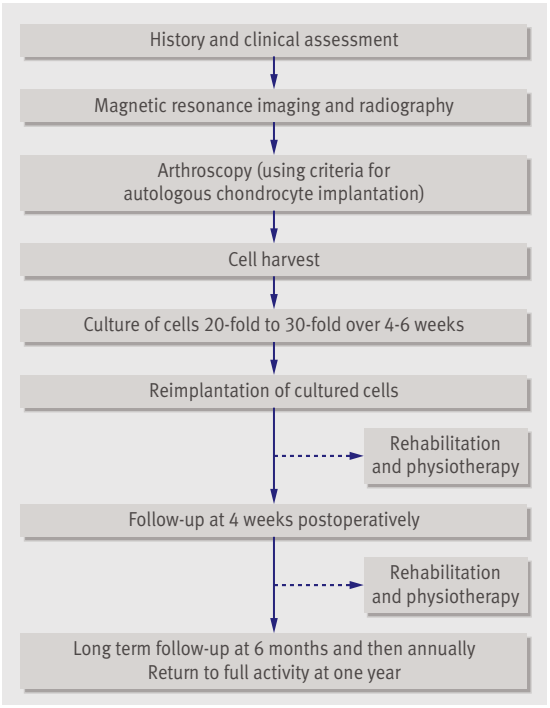

Fig 4 | Flow chart of standard protocol for autologous chondrocyte implantation in patients with suspected chondral cartilage injury in the knee

A recent cohort study has shown disturbing changes in the subchondral bone after microfracture; these include increased density and cyst formation, which delay healing and impede the load bearing function of the articular cartilage.[20]

Autologous transfers and implantation

Osteochondral autograft transplantation

Osteochondral autograft transplantation (also known as mosaicplasty) involves the transplantation of osteochondral grafts from a non-weight bearing area of the knee and transplanting them into the acquired defect (fig 2). Such transplantations were first described in 1985[w23] and made popular by Hangody in 1997.[w24] Small cylinders (4.5 mm in diameter) of harvested autologous osteochondral material are implanted into the pathological defect. This technique results in a discontinuous hyaline cartilage surface with fibrocartilage bridges between the transplanted grafts.[21] Two case series, including one observing over 700 knees, have reported good results with osteochondral autograft transplantation.[22 23 w25 w26] Failures of osteochondral autograft transplantation have included donor site morbidity when the donor site has been a source of pain; inadequate filling of the defect; poor surface congruence; and failure of the mosaic plugs to integrate with surrounding healthy cartilage.[21 24 w25 w26]

ONGOING RESEARCH

- Changing surgical techniques: the introduction of arthroscopic implantation of autologous chondrocytes,[35] reducing morbidity associated with arthrotomy
- Improving scaffolds such as matrices seeded with cultured autologous chondrocytes (MACI Genzyme, Kastrup, Denmark) and the use of 3D scaffolds in a "one step" procedure using minced cartilage suspended on an absorbable membrane[36]
- Regeneration without the use of harvested cartilage cells, such as autologous membrane induced chondrogenesis. This is a procedure similar to microfracture, whereby the "superclot" is contained by a type I/III collagen membrane possibly inducing hyaline cartilage formation[37]
- Growth factors affecting chondrocyte metabolism may promote chondral healing.[38] Growth factors such as bone morphogenic proteins are involved in the growth and differentiation of mesenchymal stem cells and thus promote differentiation and multiplication of implanted chondrocytes.[39 w31] Some concerns have been expressed about enhancement by bone morphogenic proteins in tumourgenesis[w32 w33] although the US cancer registry suggests this is not the case[w34]
- Stem cells early in the differentiation chain may be able to develop into phenotypically "normal" articular chondrocytes[w35]; some early results are promising[40]
- Genetic engineering. But the complications of short half-life of recombinant proteins and lack of effective delivery methods for intracellular-acting molecules are hurdles yet to overcome

Autologous chondrocyte implantation

Autologous chondrocyte implantation (fig 3) has been widely investigated as it may offer the best hope for repair tissue that is most similar to the articular hyaline cartilage that has been lost. Some randomised controlled comparisons and case series have reported good results using autologous chondrocyte implantation or some form of derivative of the procedure.[13 24-26 w27] Two randomised controlled studies have compared the clinical outcome of autologous chondrocyte implantation versus osteochondral autograft transplantation. The first study (100 patients) found better clinical outcomes with autologous chondrocyte implantation,[24] whereas the second study (40 patients) (evidence level II-2 according to the US Preventive Services Task Force's ranking system) found no difference in clinical outcome after two years between the two procedures.[w28]

A randomised comparison of autologous chondrocyte implantation with microfracture found similarly favourable clinical outcomes for both procedures up to five years after surgery.[17] However, a multicentre prospective comparison found better filling of the defect with autologous chondrocyte implantation than with microfracture, and improved clinical results.[27] Magnetic resonance imaging and histological analysis suggest that a better quality of repair material is achieved with autologous chondrocyte implantation than with microfracture.[17 26]

The primary aim of autologous chondrocyte implantation is to produce repair material that resembles hyaline cartilage. However, histological analysis of implanted grafts has suggested that many biopsies show fibrocartilage and mixed fibrohyaline cartilage. A comparative study of autologous chondrocyte implantation and microfracture found that the formation of this fibrous material is due to the change of cell phenotype during cell expansion and therefore the loss of chondrogenic potential of the implanted cells. This finding has led to the development of "characterised" chondrocytes that are labelled as "stable" phenotypic cells, increasing the chances of the cells maintaining their chondrogenic potential. A study series has shown a better histological profile though not one clinically superior to microfracture.[26] Most graft biopsies taken in a variety of studies have been at 12 months. Histological assessment has suggested that biopsies of grafts are taken too early and that the graft undergoes a maturation process over two years.[28] Subsequently studies have found significant evidence between the timing of biopsies of grafts, histological outcome, and clinical results, with indications that the graft continues to mature into a more hyaline-type cartilage beyond the initial 12 month stage.[29] Figure 4 shows a typical flow diagram from initial assessment of a referred patient with suspected knee chondral cartilage injury to treatment and follow-up.

Osteochondral allografts

Allografts have been used in the treatment of large chondral and osteochondral defects since the 1970s: articular cartilage is harvested from cadavers and implanted into the chondral or osteochondral defect. Prospective cohort studies have shown good results with this technique.[w29] In the United Kingdom, obtaining allografts is difficult and a small risk of disease transmission exists.

Who is the best candidate for surgery?

Microfracture has reported good results in all age groups that it has been performed on. Steadman and colleagues, however, reported better results in those aged under 35 years,[w30] and this finding has been echoed in studies of autologous chondrocyte implantation.[12] Increasing body mass index also shows a poorer correlation to success in both microfracture and autologous chondrocyte implantation,[12 30] as does smoking.[30 31]

Which treatment?

The ideal treatment of symptomatic chondral lesions would be an efficacious procedure that provides long term results with reduced morbidity and swift recovery,

TIPS FOR NON-SPECIALISTS

- Be aware that a knee effusion indicates a knee disease/disorder
- Articular cartilage injuries most commonly occur after trauma but can also occur with repetitive stress injury such as osteochondritis dissecans or softening of articular cartilage in chondromalacia patella
- Suspect an articular cartilage injury in a knee that remains painful after an index event with no other knee disease evident
- Be aware that a "normal" radiograph does not necessarily mean a normal knee
- Early referral, diagnosis, and treatment of articular cartilage injuries seem to result in better outcomes

ADDITIONAL EDUCATIONAL RESOURCES

For patients

- Cartilage damage (www.nhs.uk/conditions/Cartilage-damage/Pages/Introduction.aspx)—Information on NHS Choices website
- Cartilage damage (www.cks.nhs.uk/patient_information_leaflet/cartilage_damage)—Information on the NHS Direct website

For clinicians

- National Institute for Health and Clinical Excellence. *Autologous chondrocyte implantation (ACI) for the treatment of cartilage injury (review of existing guidance TA16)*. 2005. (Technical appraisal 89.) www.nice.org.uk/guidance/index.jsp?action=byID&r=true&o=11556
- ACTIVE trial website (Autologous Chrondrocyte Transplantation/Implantation Versus Existing treatments)—www.active-trial.org.uk/
- International Cartilage Repair Society's website—www.cartilage.org/

thus potentially preventing the possible progression to early osteoarthritis.

The current evidence does not confirm which of the current surgical procedures is best, although evidence is sufficient to support marrow stimulating techniques and autologous restorative techniques. Some surgeons advocate marrow stimulating techniques because of the ease of the procedure, its "one step" nature, reduced knee morbidity (since it can be performed arthroscopically), and relatively low cost. On the other hand, if marrow stimulating techniques have a limited longevity and a potential risk of damaging the subchondral bone it would be more beneficial to pursue restorative autologous cellular techniques despite the relatively large cost of the procedure.

In the 1990s a prospective study of 44 patients having autologous chondrocyte implantation for full thickness cartilage lesions examined the efficacy of treatment and quality of life and calculated the average cost per additional quality adjusted life year. The authors concluded that autologous chondrocyte implantation improves patients' quality of life and is therefore an appropriate, cost effective treatment for cartilage lesions of the knee.[32] However, more recently an analysis of data from randomised trials and observational studies has found insufficient evidence to show that autologous chondrocyte implantation is more cost effective than microfracture. This study did, however, show that long term results are not available but would be necessary for evaluating long term cost effectiveness.[33]

Conclusion

The current most effective management of chondral and osteochondral lesions of the knee is early diagnosis, rapid referral, and prompt treatment of serious symptomatic lesions.

Long term success must be considered in the treatment of these lesions to prevent potential early osteoarthritic changes. An early "fix" with a marrow stimulating technique may seem an attractive mid-term option, but if the repair material breaks down, leaving a knee that is in worse condition, then further surgery may be needed in the long term, with associated cost implications.

Case studies describing how early intervention with autologous chondrocyte implantation in adolescents improved their ability to return to preinjury level activity[14] show promise, in contrast to reports that failed marrow stimulating treatments reduce the rate of long term success of autologous chondrocyte implantation.[12 13]

Currently in the UK autologous chondrocyte implantation is considered only after there has been a failed "conventional" treatment (microfracture, drilling, abrasion).[34] In areas of Europe and in the United States chondrocyte implantation is offered as a first line treatment, with excellent results in those patient groups.

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1 Heir S, Nerhus TK, Røtterud JH, Løken S, Ekeland A, Engebretsen L, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. *Am J Sports Med* 2009 Dec 30. Epub ahead of print (doi:10.1177/0363546509352157)
2 Morscher E. Cartilage-bone lesions of the knee joint following injury. *Reconstr Surg Traumatol* 1971;12:2-26.
3 Mankin HJ. The response of articular cartilage to mechanical injury. *J Bone Joint Surg Am* 1982;64:460-6.
4 Buckwalter JA. Articular cartilage injuries. *Clin Orthop Relat Res* 2002;402:21-37.
5 Curl WW, Krome J, Gordon ES, Rushing BP, Smith B, Poehling G. Cartilage injuries: a review of 31 516 knee arthroscopies. *Arthroscopy* 1997;13:456-60.
6 Noyes FR, Bassett RW, Grood ES, Butler DL. Arthroscopy in acute hemarthrosis of the knee: incidence of anterior cruciate ligament tears and other injuries. *J Bone Joint Surg Am* 1980;62:687-95.
7 Krishnan SP, Skinner JA, Carrington RWJ, Flanagan AM, Briggs TWR, Bentley G. 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.
8 Bentley G. Chondromalacia patellae. *J Bone Joint Surg Am* 1970;52:221-32.
9 Oepenn RS, Connolly SA, Bencardino JT, Jaramillo D. Acute injury of the articular cartilage and subchondral bone: a common but unrecognized lesion in the immature knee. *Am J Roentgenol* 2004;182:111-7.
10 O'Driscoll SW, Keeley FW, Salter RB. The chondrogenic potential of free autogenous periosteal grafts for biological resurfacing of major full-thickness defects in joint surfaces under the influence of continuous passive motion. An experimental investigation in the rabbit. *J Bone Joint Surg Am* 1986;68:1017-35.
11 Guettler JH, Demetropoulos CK, Yang KH, Jurist KA. Osteochondral defects in the human knee: influence of defect size on cartilage rim stress and load redistribution to surrounding cartilage. *Am J Sports Med* 2004;32:1451-8.
12 Krishnan SP, Skinner JA, Bartlett W, Carrington RWJ, Flanagan AM, Briggs TWR, et al. Who is the ideal candidate for autologous chondrocyte implantation? *J Bone Joint Surg Br* 2006;88-B(1):61-4.
13 Bartlett W, Skinner JA, Gooding CR, Carrington RWJ, Flanagan AM, Briggs TWR, 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-B:640-5.
14 Mithofer K, Minas T, Peterson L, Micheli LJ. Functional outcome of knee articular cartilage repair in adolescent athletes. *Am J Sports Med* 2005;33:1147.
15 Hubbard MJ. Articular debridement versus washout for degeneration of the medial femoral condyle. A five-year study. *J Bone Joint Surg Br* 1996;78:217-19.
16 Steadman JR, Rodkey WG, Singleton SB, Briggs KK. Microfracture: surgical technique for full thickness chondral defects: technique and clinical results. *Oper Tech Orthop* 1997;7:300-4.
17 Knutsen G, Drogset JO, Engebretsen L, Gronvedt T, Isaksen V, Ludvigsen TC, 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.

18 Hunziker EB. Articular cartilage repair: basic science and clinical progress: a review of the current status and prospects. *Osteoarthritis Cartilage* 2002;10:432-63.
19 Kreuz PC, Steinwachs MR, Erggelet C, Krause SJ, Konrad G, Sudkamp N. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage* 2006;14;11:1119-25.
20 Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med* 2009;37:902-8.
21 Smith GD, Knutsen G, Richardson JB. A clinical review of cartilage repair techniques. *J Bone Joint Surg Br* 2005;87B:445-9.
22 Hangody L, Fules P. Autologous osteochondral mosaicplasty for the treatment of full thickness defects of weight bearing joints: ten years of experimental and clinical experience. *J Bone Joint Surg Am* 2003;85A(suppl II):25-32.
23 Chow JC, Hantes ME, Houle JB, Zalavras CG. Arthroscopic autogenous osteochondral transplantation for treating knee cartilage defects: a 2- to 5-year follow-up study. *Arthroscopy* 2004;20:681-90.
24 Bentley G, Biant LC, Carrington RW, Akmal M, Goldberg A, Williams AM, 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-B:223-30.
25 Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med* 1994;331:889-95.
26 Saris DB, Vanlauewe J, Victor J, Haspl M, Bohnsack M, Fortems Y, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus Microfracture. *Am J Sports Med* 2008;36:235-46.
27 Browne JE Moseley B, Erggelet C, Fu FH, Arciero RA, Micheli LJ, et al. Marrow stimulation techniques versus autologous chondrocyte implantation for treatment of full-thickness chondral defects of the knee: comparison of patient outcomes at 3-5 years. *Arthroscopy* 2003;19;6:56-6.
28 Briggs TWR, Mahroof S, David LA, Flannelly J, Pringle J, Bayliss M. Histological evaluation of chondral defects after autologous chondrocyte implantation of the knee. *J Bone Joint Surg Br* 2003; 85-B:1077-83.
29 Gikas PD, Morris T, Carrington RWJ, Skinner JA, Bentley G, Briggs TWR. A correlation between the timing of biopsy after autologous chondrocyte implantation and the histological appearance. *J Bone Joint Surg Br* 2009;91-B:997-1006.
30 Asik M, Ciftci F, Sen C, Erdil M, Atalar A. The microfracture technique for the treatment of full-thickness articular cartilage lesions of the knee: midterm results. *Arthroscopy* 24;11:1214-20.
31 Jaiswal PK, Macmull S, Bentley G, Carrington RWJ, Skinner JA, Briggs TWR. Does smoking influence outcome after autologous chondrocyte implantation? A case-controlled study. *J Bone Joint Surg Br* 91-B:12;1575-8.
32 Minas T. Chondrocyte implantation in the repair of chondral lesions of the knee: economics and quality of life. *Am J Orthop* 1998;27:739-44.
33 Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, et al. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technol Assess* 2005;9:47.
34 National Institute for Health and Clinical Excellence. Autologous chondrocyte implantation (ACI) for the treatment of cartilage injury (review of existing guidance TA16). 2005. (Technology appraisal 89.) http://guidance.nice.org.uk/TA89.
35 Abelow S, Guillen P, Ramos T. Arthroscopic technique for matrix-induced autologous chondrocyte implantation for the treatment of large chondral defects in the knee and ankle. *Op Tech Orthop* 16;4:257-61.
36 Lu Y, Dhanaraj S, Wang Z, Bradley DM, Bowman SM, Cole SJ, et al. Minced cartilage without cell culture serves as an effective intra-operative cell source for cartilage repair. *J Orthop Res* 2006;24:1261-70.
37 Anders S, Gellissen J, Zoch W, Lobenhoffer P, Grifka J, Behrens P. Autologous matrix induced chondrogenesis (AMIC) for focal chondral defects of the knee—first results. European Federation of National Associations of Orthopaedics and Traumatology (8th Congress) Florence, Italy: 11-15 May 2007.
38 O'Connor WJ, Botti T, Khan SN, Lane JM. The use of growth factors in cartilage repair. *Orthop Clin Am* 2003;31:399-410.
39 Hunziker EB. Growth-factor-induced healing of partial thickness defects in adult articular cartilage. *Osteoarthritis Cartilage* 2001;9:22-32.
40 Wakitani S, Nawata M, Tensho K, Okabe T, Machida H, Ohgushi H. Repair of articular cartilage defects in the patella-femoral joint with autologous bone marrow mesenchymal stem cell transplantation: three case reports involving nine defects in five knees. *J Tissue Eng Regen Med* 2007;1:74-9.

ANSWERS TO ENDGAMES, p 603. For long answers go to the Education channel on bmj.com

STATISTICAL QUESTION

Describing the spread of data II

Answer *c* is correct.

CASE REPORT

A pain in the leg and breathlessness

1 A serum cardiac troponin level (I or T) will help identify whether this patient is at increased risk of clinical deterioration and help guide treatment of his large pulmonary embolism.

2 Transthoracic echocardiogram specifically to check for any evidence of right ventricular dysfunction—enlargement or hypokinesis—secondary to his pulmonary embolism or residual thrombus in the right atrium or ventricle. Such findings are poor prognostic indicators.

3 This patient is currently haemodynamically stable, so he should be immediately started on low molecular weight heparin. This should be started as soon as a clinical diagnosis of venous thromboembolism is made and not after diagnostic tests have been done and the results confirmed. He should also be loaded with warfarin. From the information given there is no indication for systemic thrombolysis, because the patient does not have haemodynamic compromise.

4 Recurrent venous thromboembolism after discontinuation of anticoagulation; post thrombotic syndrome with chronic lower limb pain, oedema, and hyperpigmentation; chronic thromboembolic pulmonary hypertension where microthrombi and vascular remodelling results in increased resistance to pulmonary blood flow, raised pulmonary artery pressures, and eventually right ventricular failure.