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Total joint replacement of hip or knee as an outcome measure for structure modifying trials in osteoarthritis

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Summary

Objective: The Group for the Respect of Ethics and Excellence in Science (GREES) organized a working group to assess the value of time to joint surgery as a potential therapeutic failure outcome criterion for osteoarthritis (OA) of the hip or knee in the assessment of potential structure modifying agents.

Methods: PubMed was searched for manuscripts from 1976 to 2004. Relevant studies were discussed at a 1-day meeting.

Results: There are no accepted guidelines for 'time to' and 'indications for' joint replacement surgery. A limited number of trials have examined joint replacement surgery within the study population. Several parameters, particularly joint space narrowing (interbone distance), correlate with surgical intervention. However, at the level of the knee, none of the parameters have positive predictive value for joint replacement

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surgery better than 30%. In contrast, lack of significant joint space narrowing has a strong negative predictive value for joint replacement surgery (>90%), that remains after controlling for OA pain severity.

Conclusion: At this time, GREES cannot recommend time to joint surgery as a primary endpoint of failure for structure modifying trials of hip or knee OA—as the parameter has sensitivity but lacks specificity. In contrast, in existing trials, a lack of progression of joint space narrowing has predictive value of >90% for not having surgery. GREES suggests utilizing joint space narrowing (e.g., >0.3–0.7 mm) combined with a lack of clinically relevant improvement in symptoms (e.g., ≥ 20–25%) for 'failure' of a secondary outcome in structure modifying trials of the hip and knee.

Key words: GREES, Structure modifying trials for osteoarthritis, Randomized clinical trials, Disease modification, Joint replacement surgery, Joint space narrowing.

Introduction

Until recently, therapy of osteoarthritis (OA) has been directed at symptoms, primarily pain. There is a concerted effort to study new and established agents for their potential to alter the course of OA[1,2]. Regulatory agencies have recognized that there is a potential for an agent to interfere with the structural progression (disease modification) of OA[3,4]. To date, a variety of surrogate outcome criteria have been examined for hip and knee OA including markers of cartilage and/or bone metabolism and imaging of joint space narrowing (interbone distances)[1,5].

Although joint space narrowing on a standardized radiograph is an appropriate primary endpoint, it is apparent to the regulatory agencies that a reliable clinical endpoint would be more desirable. Development of potential structure modifying agents has been hampered by the lack of a generally accepted and validated clinical outcome to fill this role.

Prevention, or delay, to joint replacement surgery is an attractive outcome measure of clinical disease progression (Table I). We address the potential utility of 'time to joint replacement' as a variable in the measurement of progression of OA of the hip or knee.

Table I
Lower extremity joint surgery as an outcome in structure modifying trials of osteoarthritis of the hip or knee

Joint replacement as an attractive outcome criteria
Large numbers of surgical procedures
Patients opt to non-surgical interventions
Financial burden of surgery and rehabilitation
Risk of general surgery
Factors that may predispose to total joint replacement
Advancing age
Women > men
Severe pain
Disability (e.g., Algofunctional index)
Progressive joint space narrowing (interbone distance) on radiography
Factors influencing the time to performing joint replacement surgery
Regional variations[6,7]
Women more than men[6,7]
Related to population density[6]
Lack of correlation to number of surgeons[6]
Tend to dependency on demographics (e.g., income, sex, age, race)[7]
Health policy
Level of pain
Level of disability
Inequity in waiting times[8]
Insurance carrier vs single carrier insurance vs out of pocket payment
Rationing by Health Maintenance Organizations[9]

Method

The Group for the Respect of Ethics and Excellence in Science (GREES) ''Section Osteoarthritis'', met on March 12, 2004. The GREES includes academic scientists with an extensive background in the considered field (i.e., rheumatology, public health, radiology, biochemistry, epidemiology and health economics), members of European national regulatory authorities and representatives of the pharmaceutical industry. A subgroup of the GREES (BA, OB, J-YR) performed an extensive search of the Medline electronic database from 1977 until 2004. Keywords included ''indication for total joint replacement'', ''time to total joint replacement'', ''outcome in osteoarthritis''. In addition, Medline was searched by the names of several prominent clinical research investigators with an interest in outcome in OA. Since not all data are indexed in the electronic databases, we conducted a hand search of the reference section of each of the articles retrieved by the primary search until no new paper was found. We also contacted GREES members (scientists or industrial partners) active in OA. The invited experts made a critical analysis of the available science. The objective was to provide regulatory authorities with a reference on their evaluation of guidelines for registration of agents for therapy of structure modification in OA.

Manuscripts were screened for indications for 'total joint replacement' and 'time to joint replacement surgery'. The search was limited to the hip and knee. Only English language manuscripts were reviewed.

Results

CURRENT REGULATORY GUIDELINES

Existing regulatory guidelines for the approval of drugs to be used as structure modifying drugs for the treatment of OA have been published in the United States and in Europe[3,4]. The US FDA guidelines state that 'time to joint surgery' is an acceptable outcome for structure modifying drugs[3]. Similarly, the European Committee for Proprietary Medicinal Products (CPMP) guidelines state that even though a structure modifying drug may not have an independent effect on symptoms, clinical signs and symptoms need to be assessed[4]. Hence, both United States and European guidelines encourage delay in 'time to joint surgery' to be examined in clinical trials of structure modifying drugs.

OUTCOMES OF RECENT CLINICAL TRIALS WITH STRUCTURE MODIFYING DRUGS

A limited number of clinical trials have examined the relationship of 'time to joint surgery' as an outcome parameter[10,11]. These publications report the results

Table II
Glucosamine sulphate structure modifying trial follow-up[11,13]

Subsets 3 year trial (*N*)	Placebo 106	Glucosamine 106	Total 212
5 year follow-up (*N*)			
Died	8	12	20
Lost to follow-up	12	3	15
Clinic follow-up	43	58	101
5 year follow-up Lower limb OA-related surgery (*N*)			
Any surgery hip or knee†	17	9	26
Any surgery knee‡	14	8	22
TJR§	12	7	19

TJR = total joint replacement hip or knee.
†RR 0.52; $P = 0.06$.
‡RR 0.54; $P = 0.13$.
§RR 0.55; $P = 0.18$.

obtained after treatment of hip or knee OA patients with diacerein and glucosamine sulphate.

Several but not all[12] clinical studies demonstrate the clinical effectiveness of glucosamine sulphate in OA, particularly of the knee. Two 3 year studies demonstrated a reduction on joint space narrowing of the medial compartment of the knee when comparing glucosamine sulphate to placebo treated patients (Tables II and III)[13,14]. A 5 year follow-up was conducted to assess long-term outcomes after treatment discontinuation, including the occurrence of OA-related joint surgery, evolution of radiographic knee joint structure changes and symptoms, quality of life and the pharmacoeconomic impact on the use of health resources[11]. Patients on glucosamine sulphate for 3 years had a significantly smaller radiographic joint space narrowing and still exhibited an improvement on pre-trial scores of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) Algofunctional index at the 5 year follow-up. Finally, quality of life Short Form (SF)-36 scores were better in the glucosamine sulphate treated patients. A pharmacoeconomic questionnaire suggested that the glucosamine sulphate treated patients used fewer health resources during the previous year.

Diacerein may be an interleukin (IL)-1β inhibitor. In clinical trials, diacerein was shown to reduce pain and functional impairment in patients with hip or knee OA (Tables IV and V)[15]. In the 3 year Evaluation of the Chondromodulating Effect of Diacerein in Osteoarthritis of the Hip (ECHODIAH) study[10], diacerein was evaluated for its effect on the progression of joint space narrowing in patients with hip OA. The study achieved three of the four primary endpoints that measured radiographic progression of hip OA. Although there was no difference in mean joint space narrowing for the intent-to-treat population between diacerein and placebo, there was significantly less progression in mean joint space narrowing for the complete analysis. In addition, there were significantly fewer patients with radiographic joint space narrowing of at least 0.5 mm at any time during the study period when comparing diacerein treated patients to those on placebo. In relation to total hip replacement (THA) surgery, there was a trend towards fewer patients undergoing THA procedures in the diacerein group when compared to the placebo group.

CRITERIA FOR TOTAL JOINT REPLACEMENT

Despite the success of total joint replacement of the hip and knee over the last 30+ years, the criteria for when to perform such surgery are not clear. THA is an option for nearly all patients with diseases of the hip that cause chronic discomfort and/or significant functional impairment[16]. At a National Institutes of Health sponsored workshop, the following statement was issued: "NIH Consensus Statement concluded that candidates for THA should have moderate to severe persistent pain, disability, or both, not substantially relieved by an extended course of non-surgical management in association with radiographic signs of OA"[16–18].

The level of pain needed to indicate surgery is appropriate is unclear. In two Canadian pre-operative evaluations of 188 and 163 patients with hip OA, the average mean WOMAC pain subscale scores by visual analog scale (VAS) were 53 ± 17SD mm and 57 ± 16 mm[19,20]. The day before THA the mean WOMAC pain subscale score was 55 ± 17 mm in 74 patients from Sweden[21]. In the Netherlands, 62 patients averaged 63 ± 25 mm in a VAS pain score while waiting for THA[22]. Similar results were obtained in the ECHODIAH study where the mean VAS was 56 ± 17 mm prior to surgery in 135 patients undergoing THA (Table IV). Although these numbers appear reasonably consistent, many patients were on analgesic and/or anti-inflammatory drugs. In addition, there is no separation in the level of pre-operative pain for those undergoing joint replacement surgery and the level of pain in the majority of reported clinical trials for those who do not have immediate plans for joint replacement surgery.

A United Kingdom study evaluated the relationship of disability to joint replacement study of 249 patients in the post-operative period. They found that pre-operatively

Table III
Joint space narrowing as a predictor of knee surgery in glucosamine sulphate 5 year follow-up[11,13]

JSN (mm)	Prevalence (%)	RR (95% CI)	*P*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall efficacy (%)
≥ 0.2	42	3.01 (1.09–8.26)	0.03	63	60	19	92	62
≥ 0.3	40	3.43 (1.24–9.53)	0.017	63	64	20	92	66
≥ 0.4	37	3.88 (1.39–10.86)	0.009	63	67	22	93	69
≥ 0.5	32	4.61 (1.65–12.84)	0.003	63	73	25	93	73
≥ 0.6	29	5.16 (1.76–15.12)	0.003	61	76	28	93	77
≥ 0.7	26	5.15 (1.70–15.60)	0.004	63	79	30	94	79
≥ 0.8	24	4.83 (1.64–14.20)	0.004	50	80	27	92	78

Adjusted for age, body-mass index, total WOMAC, baseline minimal JSW. JSN = minimal joint space narrowing; RR = relative risk; $P = P$ value; PPV = positive predictive value or percent ability of JSN to predict knee surgery; NPV = negative predictive value or the lack of the ability of JSN to predict knee surgery.

Table IV
Total hip arthroplasty (THA) in patients within 6 months of completion of a 3 year trial of diacerein[10]

	+THA ($n = 135$)	−THA ($n = 372$)	*t*-Test (*P* value)
VAS pain (mm)			
Mean (SD)	55.8 (17.5)	33.7 (18.4)	<0.0001
Maximum (SD)	79.4 (15.8)	59.4 (20.1)	<0.0001
Algofunctional index (0−24)			
Mean (SD)	9.2 (2.7)	6.0 (2.6)	<0.0001
Maximum (SD)	13.6 (3.5)	9.3 (2.9)	<0.0001
Algofunctional index			
≥ 12 (*N*)	95	68	
<12 (*N*)	40	304	
VAS handicap (mm)			
Mean (SD)	55.5 (19.1)	32.6 (19.4)	<0.0001
Maximum (SD)	81.4 (15.9)	61.5 (22.5)	<0.0001
Narrowest joint space width			
Mean (SD)	1.23 (0.8)	2.18 (0.9)	<0.0001
Maximum (SD)	0.69 (0.9)	1.84 (1.0)	<0.0001

+THA = Total hip arthroplasty performed; −THA = Total hip arthroplasty not performed; Algofunctional index of Lequesne (see text).

62% were handicapped but independent and 26% were partially dependent[23]. The WOMAC physical function subscale averaged 60 ± 16SD mm in 188 Londoners, 61 ± 15SD mm in 163 Canadians, and 61 ± 15SD mm in 74 patients from Sweden[19–21]. The mean Lequesne Algofunctional Index just prior to THA in 126 patients from the ECHODIAH study was 12.6 ± 4.3 mm (baseline values from the overall ECHODIAH study were 9.2 ± 2.7 mm). In a study of 72 patients undergoing THA from the United States, 79% had lost ≥ 50% of their functional capacity between the beginning of symptoms to the time of surgery[24]. These latter studies record change in function prior to surgery, but no amount of change was proposed to suggest the need for or indication of surgery. In the ECHODIAH study, the higher baseline values for symptoms were strongly correlated with total joint arthroplasty ($P < 0.0001$)[25].

The overall clinical severity of OA examined in 2124 patients undergoing THA was 56 mm (average) in the total WOMAC from the United Kingdom Hip and Knee Register[26]. In the ECHODIAH study, both change in VAS for pain and worsening Lequesne Algofunctional Index predicted the occurrence of surgery[25].

Global scores for the indication for THA have been proposed, but limited validation has been published[27–29].

It appears that there is considerable variation in the time to surgery among surgeons. Time to surgery is influenced by many factors (Table I), and variation exists between countries, cities within countries, and surgeons within the same institution. The rate of hip replacement surgery increases with age until age 75, when it declines[30]. Women and whites had higher rates of THA than men and African−Americans.

There has been a recent appreciation of the predictive value of high signal bone marrow lesions (previously called bone edema) with the progression of OA of the knee[31]. Additional studies are needed to determine the sensitivity and specificity of this finding in predicting joint replacement surgery.

Several groups have been formed in an attempt to set up criteria to determine when joint replacement surgery would be indicated[27–29,32,33].

Table V
Predictive values for total hip arthroplasty in patients within 6 months of completion of a 3 year trial of diacerein[10]

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
VAS pain ≥ 70 mm	78	66	45	89
Algofunctional index ≥ 12	70	82	58	88
VAS handicap ≥ 70 mm	79	56	40	88
Narrowest joint space width ≤ 1 mm	73	74	51	88

JOINT SPACE WIDTH AS A CRITERION FOR JOINT REPLACEMENT SURGERY

A retrospective analysis of knee OA examined the outcome of 1507 patients with serial extended weight bearing knee radiographs[34]. They defined patients as a 'failure' if they reached a rating of 3 for joint space width using an atlas of radiographs. The Kaplan−Meier survival analysis used time to reach the rating of 3 from baseline. They also rated a 'failure' if the patient underwent total joint replacement; they then combined the two 'failure' groups. In COX regression analysis, initial joint space width, body-mass index (BMI), symptom duration and global severity were predictors of progression. The strongest predictor of 'failure' was reduced baseline joint space width, even after adjustment for pain.

A study of 423 patients followed for 5 years evaluated decrease in joint space width. For years 1 and 2 there was a reduction of 0.2 and 0.4 mm, with a relative reduction of 15 and 20%, respectively. This resulted in a prediction of THA specificity of 67−68% and sensitivity of 68−75%[35].

CLINICAL TRIALS THAT HAVE EXPLORED TIME TO SURGERY

A limited number of studies have examined time to surgery as a criterion for effectiveness of a structure modifying drug[10,11].

Glucosamine sulphate was studied in two 3 year clinical trials for structure modification[13,14]. As above, one of the trials has a 5 year follow-up available that examines symptoms, quality of life, the pharmacoeconomic impact on use of health resources, radiographic knee joint structural changes and the occurrence of OA-related joint surgery (Tables II and III)[11]. Of the original 212 patients with knee OA, 177 (83%) could be contacted and queried about their arthritis (Table II). Lower limb surgery was performed on 27 patients with total knee or hip surgery performed in 19 (Table III). Despite small numbers, there was a trend toward a difference between those on placebo vs glucosamine sulphate for lower limb OA-related surgery ($P = 0.06$).

Reduction in minimum joint space width and sex (women) were predictors of the need for joint surgery in two models of logistic regression ($P = 0.004$−0.007). The model includes minimal joint space width at baseline with BMI, age, total WOMAC, change in total WOMAC, pain subscale of the WOMAC and change in pain subscale of the WOMAC. The overall efficiency of minimal but not mean joint space narrowing to predict those going to surgery is demonstrated in Table III. Although the relative risk, *P* values and predictive values suggest progressive reduction

Table VI
Joint space narrowing with pain as a predictor of knee surgery in glucosamine sulphate 5 year follow-up[11,13]

JSN pain† (mm)	Prevalence *N* (%)	RR (95% CI)	*P*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall efficacy (%)
≥ 0.5	69/122 (54)	4.99 (1.18–21.18)	0.012	87	48	19	96	55
≥ 0.7	66/122 (54)	5.52 (1.30–23.41)	0.007	87	50	20	96	57

Adjusted for age, body-mass index, total WOMAC, baseline minimal JSW. JSN = minimal joint space narrowing; RR = relative risk; $P = P$ value; PPV = positive predictive value or percent ability of JSN to predict knee surgery; NPV = negative predictive value or the lack of the ability of JSN to predict knee surgery.

†Pain = improvement of $\leq$20% in WOMAC pain subscale.

in minimal joint space narrowing is predictive of those going to joint surgery for the knee, the specificity is lost with the predictive value not higher than 30%.

Further analysis of the two glucosamine sulphate studies allows combining symptom response with joint space narrowing (Table VI)[13,14]. For a failure definition of joint space narrowing of ≥ 0.5 mm and $<$20% improvement in the WOMAC pain subscale of 20%, there would be 55/133 (41%) failures with glucosamine sulphate vs 74/124 (60%) on placebo ($P = 0.003$).

The ECHODIAH trial was a 3 year, multicenter, prospective study designed to evaluate the structural effect of diacerein vs placebo on OA of the hip. Patients were evaluated every 3 months and radiographs were obtained yearly. A *post-hoc* analysis examined those undergoing THA within 6 months of completion of the 3 year study. This was compared with those not undergoing THA in the same time period (Tables IV and V). Although the negative predictive values were near 90%, the best positive predictive value was the Lequesne Algofunctional index of ≥ 12 at 58%—consistent with the above glucosamine sulphate study results.

Discussion

Although attractive as a "hard" clinical outcome for the failure of drug in a structure modifying trials for OA of the hip and knee, time to joint surgery as a variable has been hampered by inconsistency in the decision on when to perform surgery, the lack of standardized guidelines for when to perform surgery and the lack of adequate number of studies that examine joint surgery as an endpoint in structure modifying trials. Hence, GREES is reluctant to recommend 'time to joint surgery' as a primary endpoint for OA of the hip and knee extremity surgery until there is additional data validating this method.

However, at this time, the specificity and sensitivity of existing data suggest that criteria, such as lack of progressive joint space narrowing is predictive of not going to surgery. The negative predictive value of this outcome is over 90% for any of the selected cutpoints between 0.3 and 0.7 mm in the glucosamine sulphate studies.

There have been several attempts to develop guidelines for when to perform joint replacement surgery. Few are supported by research. Support for the negative predictive value of a variety of measurements for joint replacement is from a study on a composite index for THA[29]. The group studied 466 patients with clinical and radiographic data. Their composite index had a positive predictive value of 54% and a negative predictive value of 87%. They concluded that the index was of value in selecting those patients who should not be referred for THA.

There are a variety of issues not raised by the existing clinical trials. Clinical trials—by design—have selected populations, and probably do not reflect the general population. Some of the issues are noted:

- Differences in the design of clinical trials tend to select different populations of patients: e.g., a structure modifying trial would tend to include less severely symptomatic patients than a short-term anti-inflammatory agent trial.
- Time to joint replacement may be different in these two populations. Since there are no generally accepted criteria for joint replacement surgery, patients entering the trial may already be candidates for joint replacement surgery; hence, going to surgery during the trial introduces bias. Conversely, patients entering a long-term structure modifying trial may be doing so with a very strong desire (more than the usual) to avoid surgery.
- The majority of patients with OA do not progress very rapidly to joint replacement surgery, increasing the sample size required to demonstrate a difference between therapy and placebo.
- There is a subset of patients with a rather rapid progression of OA that will come to surgery more quickly than the overall study population. At present, there are no clinical markers to identify this population at the onset of the trial.
- Patients are generally selected on the basis of Kellgren Lawrence grade II or III. At present, there is no good clinical correlation to the pathologic findings with these classifications. They probably represent a variety of populations that may or may not respond to the same therapy.
- There are differences in the progression of OA in hip and knee. Will a structure modifying agent have an equal effect on delaying surgery in these two groups? Will separate studies need to be conducted?

The multiple complicating factors that influence time to joint surgery have not been adequately separated and studied. New studies on structure modifying agents need to include time to joint surgery as a secondary efficacy parameter for failure of the study drug in order to develop a better understanding of the relevance of this observation.

At this stage, the GREES recommends that 'failure' as a secondary endpoint be included in clinical trials of structure management of OA of the lower limbs. 'Failure' is defined as an individual developing progression of minimal joint space narrowing (threshold over a minimal of 0.3 and 0.7 mm) and without a clinically relevant symptomatic benefit (i.e., 20–25% improvement on the WOMAC pain subscale).

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References

1. Altman RD, Bloch DA, Dougados M, Hochberg M, Lohmander S, Pavelka K, *et al*. Measurement of structural progression in osteoarthritis of the hip: the Barcelona consensus group. Osteoarthritis Cartilage 2004;12:515–24.
2. Reginster JY, Bruyere O, Henrotin Y. New perspectives in the management of osteoarthritis structure modification: facts or fantasy? J Rheumatol 2003;30: 14–20.
3. Guidance for the industry. Clinical development programs for drugs, devices and biological products intended for the treatment of osteoarthritis. US Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research, July 1999. Available from: http://www.fda.gov/cder/guidance/2199dft.htm.
4. Points to consider on clinical investigation of medicinal products used in the treatment of osteoarthritis. European Agency for the Evaluation of Medicinal Products. Committee for Proprietary Medicinal Products, July 1998. Available from: http://www.emea.eu.int/pdfs/human/ewp/078497en.pdf.
5. Abadie E, Ethgen D, Avouac B, Bouvenot G, Branco J, Bruyere O, *et al*. Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. Osteoarthritis Cartilage 2004;12:263–8.
6. Dieppe P, Basler HD, Chard J, Croft P, Dixon J, Hurley M, *et al*. Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. Rheumatology 1999; 38:73–83.
7. Skinner J, Weinstein JN, Sporer SM, Wennberg JE. Racial, ethnic, and geographic disparities in rates of knee arthroplasty among medicare patients. N Engl J Med 2003;349:1350–9.
8. Kelly KD, Voaklander DC, Johnston WC, Suarez-Almazor ME. Equity in waiting times for major joint arthroplasty. Can J Surg 2002;45:269–76.
9. Morgan RO, Virnig BA, DeVito CA, Persily NA. Medicare HMO disenrollment and selective use of medical care: osteoarthritis-related joint replacement. Am J Manage Care 2000;6:917–23.
10. Dougados M, Nguyen M, Berdah L, Mazieres B, Vignon E, Lequesne M, for the ECHODIAH Investigator Study Group. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis. Arthritis Rheum 2001;4:2539–47.
11. Bruyere O, Compère S, Rovati LC, Giacovelli G, Deroisy R, Reginster JY. Five-year follow-up of patients from a previous 3 year randomized, controlled trial of glucosamine sulfate in knee osteoarthritis. Arthritis Rheum 2003;48(Suppl):80.
12. McAlindon T. Why are clinical trials of glucosamine no longer uniformly positive? Rheum Dis Clin North Am 2003;29:789–801.
13. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, *et al*. Long-term effect of glucosamine sulfate on osteoarthritis progression: a randomized placebo-controlled clinical trial. Lancet 2001;27: 251–65.
14. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulphate delays progression of knee osteoarthritis: a 3-year, randomized placebo-controlled, double-blind study. Arch Intern Med 2002;162:2113–23.
15. Pelletier JP, Yaron M, Haraoui B, Cohen P, Nahir MA, Choquette D, *et al*. Efficacy and safety of diacerein in osteoarthritis of the knee. Arthritis Rheum 2000;43: 2339–48.
16. NIH Consensus Conference. NIH Consensus Development Panel on Total Hip Replacement. JAMA 1995; 273:1950–6.
17. National Institutes of Health Consensus Statement in total knee replacement. December 8–10, 2003. Available at: http://consensus.nih.gov/cons/117/117cdc_statement2.htm.
18. Maloney JM, Berry DJ. Lower extremity considerations: hip. In: Moskowitz RW, Howell DS, Altman RD, Buckwalter J, Goldber V, Eds. Osteoarthritis Diagnosis and Medical/Surgical Management. Philadelphia, PA: Saunders 2001;507–22.
19. Laupacis A, Bourne R, Rorabeck C, Feeny D, Wong C, Tugwell P, *et al*. The effect of elective total hip replacement on health-related quality of life. J Bone Joint Surg 1993;75A:1619–26.
20. Allyson Jones C, Voaklander DC, Johnston WC, Suarez-Almazor ME. The effect of age on pain, function, and quality of life after total hip and knee arthroplasty. Arch Intern Med 2001;161:454–60.
21. Nilsdotter AK, Aurell Y, Sjosteen AK, Lohmander LS, Roos HP. Radiographic stage of osteoarthritis or sex of the patient does not predict one year outcome after total hip arthroplasty. Ann Rheum Dis 2001;60: 228–32.
22. Borstlap M, Zant JL, Van Soesbergen RM, Ven Der Korst JK. Quality of life assessment: a comparison of four questionnaires for measuring improvements after total hip replacement. Clin Rheumatol 1995;14: 15–20.
23. Chitnavis J, Sinsheimer JS, Suchard MA, Clipsham K, Carr AJ. End-stage coxarthrosis and gonarthrosis. Aetiology, clinical patterns and radiological features of idiopathic osteoarthritis. Rheumatology 2000;39: 612–9.
24. Wright JG, Young NL. The Patient-Specific Index: asking patients what they want. J Bone Joint Surg Am 1997;79-A:974–83.
25. Dougados M, Guegen A, Nguyen M, Berdah L, Lequesne M, Mazieres B, *et al*. Requirement for total hip arthroplasty: an outcome measure of hip osteoarthritis? J Rheumatol 1999;26:855–61.
26. http://www.lenfunk.btinternet.co.uk.
27. Lequesne M. The algofunctional indices for hip and knee osteoarthritis. J Rheumatol 1997;24:779–81.
28. Hadorn HC, Holmes AC. Education and debate: the New Zealand priority criteria project. Part I: overview. BMJ 1997;314:131–4.
29. Maillefert JF, Gueguen A, Nguyen M, Berdah L, Lequesne M, Mazieres B, *et al*. A composite index

for total hip arthroplasty in patients with hip osteoarthritis. J Rheumatol 2002;29:347–52.
30. Mohamed NN, Barrett JA, Katz JN, Phillips CB, Losina E, Lew RA, *et al*. Rates and outcomes of primary and revision total hip replacement in the United States medicare population. J Bone Joint Surg Am 2003;85-A: 27–32.
31. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, *et al*. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003;139:330–6.
32. Hawker GA, Wright JG, Coyte PC, Williams JI, Harvey B, Glazier R, *et al*. Differences between men and women in the rate of use of hip and knee arthroplasty. N Engl J Med 2000;342:1016–22.
33. NIH consensus development panel on total hip replacement. JAMA 1995;273:1950–6.
34. Wolfe F, Lane N. The longterm outcome of osteoarthritis: rates and predictors of joint space narrowing in symptomatic patients with knee osteoarthritis. J Rheumatol 2002;29:139–46.
35. Maillefert JF, Gueguen A, Nguyen M, Berdah L, Lequesne M, Mazieres B, *et al*. Relevant change in radiological progression in patients with hip osteoarthritis. I. Determination using predictive validity for total hip arthroplasty. Rheumatology (Oxford) 2002;41:142–7.