

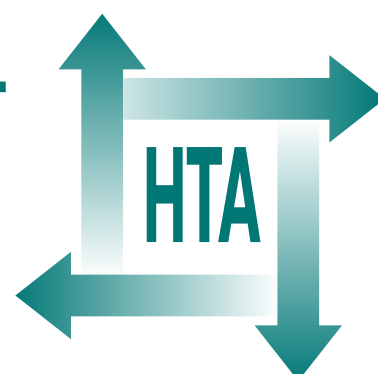
The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation

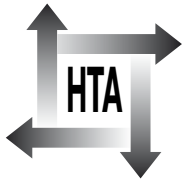
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The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 07/61/01. The protocol was agreed in February 2008. The assessment report began editorial review in December 2008 and was accepted for publication in March 2009. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation

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Objective: To assess the clinical effectiveness and cost-effectiveness of glucosamine sulphate/hydrochloride and chondroitin sulphate in modifying the progression of osteoarthritis (OA) of the knee.

Data sources: Electronic databases were searched from 1950 to 2008 and included: MEDLINE and PubMed; EMBASE; Cochrane Library (including Cochrane Systematic Reviews Database, CENTRAL, DARE, NHS EED and HTA databases); Allied and Complementary Medicine (AMED); National Research Register (NRR); Web of Science Proceedings; Current Controlled Trials; and ClinicalTrials.gov. Other sources included bibliographies of retrieved papers, registered but unpublished trials, internet searches and the Food Standards Agency website.

Review methods: A search was conducted for systematic reviews of randomised controlled trials (RCTs), which were used to identify RCTs of at least 12 months' duration and updated with searches for primary studies. A cost-effectiveness model was constructed using cohort simulation and drawing on available evidence. Sensitivity analysis was undertaken and value of information analysis conducted. A review of studies of mechanism of action was carried out to explore the biological plausibility of the preparations.

Results: Five systematic reviews and one clinical guideline met the inclusion criteria. They reported inconsistent conclusions with only modest effects on reported pain and function. A reduction in joint space narrowing was more consistently observed, but the effect size was small and the clinical significance uncertain. A separate review of eight primary trials of

> 12 months' duration showed evidence of statistically significant improvements in joint space loss, pain and function for glucosamine sulphate, but the clinical importance of these differences was not clear. In two studies of glucosamine sulphate, the need for knee arthroplasty was reduced from 14.5% to 6.3% at 8 years' follow-up. For other preparations of glucosamine, chondroitin and combination therapy, there was less evidence to support a clinical effect. Cost-effectiveness modelling was restricted to glucosamine sulphate. Over a lifetime horizon the incremental cost per quality-adjusted life-year (QALY) gain for adding glucosamine sulphate to current care was estimated to be £21,335. Deterministic sensitivity analysis suggested that the cost-effectiveness of glucosamine sulphate therapy was particularly dependent on the magnitude of the quality of life (QoL) gain, the change in knee arthroplasty probability with therapy and the discount rate. At a cost per QALY gained threshold of £20,000, the likelihood that glucosamine sulphate is more cost-effective than current care is 0.43, while at a threshold of £30,000, the probability rises to 0.73. Probabilistic sensitivity analysis showed that estimates were imprecise and subject to a degree of decision uncertainty. Value of information analysis demonstrated the need for further research. Several biologically plausible mechanisms of action for glucosamine sulphate and chondroitin were proposed. **Conclusions:** There was evidence that glucosamine sulphate shows some clinical effectiveness in the treatment of OA of the knee. No trial data came from the UK and caution should be exercised in generalising the findings to the UK health-care setting. Cost-

effectiveness was not conclusively demonstrated. There was evidence to support the potential clinical impact of glucosamine sulphate. The value of information analysis identified three research priorities: QoL, structural outcomes and knee arthroplasty. The biological

mechanism of glucosamine sulphate and chondroitin remains uncertain and, in particular, the proposal that the active substance may be sulphate should be explored further.



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List of abbreviations

ACR	American College of Rheumatology	mRNA	messenger ribonucleic acid
BMI	body mass index	NCCCC	National Collaborative Centre for Chronic Conditions
BNF	<i>British National Formulary</i>	NICE	National Institute for Health and Clinical Excellence
CI	confidence interval	NO	nitric oxide
COX	cyclo-oxygenase	NSAID	non-steroidal anti-inflammatory drug
CRD	Centre for Reviews and Dissemination	OA	osteoarthritis
EVPI	expected value of perfect information	OARSI	Osteoarthritis Research Society International
FDA	Food and Drug Administration	OMERACT	outcome measurement in clinical trials
GAIT	Glucosamine/chondroitin Arthritis Intervention Trial	PGE ₂	prostaglandin E ₂
ICER	incremental cost-effectiveness ratio	PPP	purchasing power parity
IL	interleukin	QALY	quality-adjusted life-year
iNOS	inducible nitric oxide synthase	QoL	quality of life
INR	international normalised ratio	QUOROM	quality of reporting of meta-analyses
JOA	Japan Orthopaedic Association	RCT	randomised controlled trial
MCID	minimal clinically important difference	RR	relative risk
MHRA	Medicines and Healthcare Products Regulatory Agency	SD	standard deviation
MMP	matrix metalloproteinase	SE	standard error
MRI	magnetic resonance imaging	SF-36	36-item Short Form General Health Survey

continued

TKR	total knee replacement
TNF	tumour necrosis factor
VAS	visual analogue scale

WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities osteoarthritis index

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

Osteoarthritis (OA) of the knee is a major source of disability in the UK, resulting in pain, loss of function and, for some, the need for knee arthroplasty. Two components of cartilage structure, glucosamine and chondroitin, are available as food supplements and/or licensed medicines. Reviews of short-term effectiveness in preventing disease progression and symptom control have been disappointing.

Objective

The aim of this systematic review and economic analysis was to assess the clinical effectiveness and cost-effectiveness of glucosamine sulphate or hydrochloride and chondroitin sulphate in modifying the progression of OA of the knee.

Methods

To assess clinical effectiveness, we first conducted a search for systematic reviews of randomised controlled trials (RCTs). Electronic databases were searched from 1950 to 2008 and included: MEDLINE and PubMed; EMBASE; Cochrane Library (including Cochrane Systematic Reviews Database, CENTRAL, DARE, NHS EED and HTA databases); Allied and Complementary Medicine (AMED); National Research Register (NRR); Web of Science Proceedings; Current Controlled Trials; and ClinicalTrials.gov. Other sources included bibliographies of retrieved papers, registered but unpublished trials, internet searches and the Food Standards Agency website. We used these reviews to identify RCTs of at least 12 months' duration and updated our findings with searches for primary studies up to October 2007, with monthly alerts being checked through to November 2008. Data were extracted from the reviews and RCTs and quality was checked. Where appropriate, meta-analysis was undertaken.

No cost-effectiveness studies were identified in the published literature. Using cohort simulation, and drawing on evidence from the clinical effectiveness

review as well as from other relevant sources, a model to assess cost-effectiveness was constructed. Sensitivity analysis was undertaken and value of information analysis conducted.

Furthermore, a review of studies of mechanism of action was carried out to explore the biological plausibility of the preparations under study.

Results

Five systematic reviews and one clinical guideline met the inclusion criteria. They reported inconsistent conclusions with, at best, modest effects on reported pain and function. A reduction in joint space narrowing was more consistently observed; however, the effect size was small and the clinical significance was reported to be uncertain. Data were not presented separately for long-term studies of > 12 months; therefore, we went on to review separately RCTs of > 12 months' duration.

Eight primary trials were included with a duration of at least 12 months. There was evidence of statistically significant improvements in joint space loss, pain and function for glucosamine sulphate; however, the clinical importance of these differences was less clear. In two studies of glucosamine sulphate, both funded by the manufacturer (Rotta, Italy) of an oral powder product, the need for knee arthroplasty was reduced from 14.5% to 6.3% at 8 years' follow-up. For other preparations of glucosamine, chondroitin and combination therapy, there was less evidence to support a clinical effect.

Cost-effectiveness modelling was restricted to glucosamine sulphate. Over a lifetime horizon the incremental cost per quality-adjusted life-year (QALY) gain for adding glucosamine sulphate to current care was estimated to be £21,335. Deterministic sensitivity analysis suggested that the cost-effectiveness of glucosamine sulphate therapy was particularly dependent on the magnitude of the quality of life (QoL) gain. At a cost per QALY gained threshold of £20,000, the likelihood that glucosamine sulphate is more cost-effective than current care is 0.43, while at a threshold of

£30,000, the probability rises to 0.73. Probabilistic sensitivity analysis showed that estimates were somewhat imprecise and subject to some degree of decision uncertainty. Value of information analysis indicated that further research to reduce decision uncertainty would be beneficial, with priority being given to determining the magnitude and duration of QoL gains that arise following treatment.

Several biologically plausible mechanisms of action for glucosamine sulphate and chondroitin were proposed. Importantly, bioavailability in the joint space synovial fluid was demonstrated.

Conclusions

There was evidence that glucosamine sulphate shows some clinical effectiveness in the treatment of OA of the knee. No trial data came from the UK, and in the absence of good UK data about the current referral practice, management and surgical rate, caution should be exercised in generalising these data to the UK health-care setting. Cost-effectiveness was not conclusively demonstrated, with substantial uncertainty related to the magnitude and duration of QoL gain following treatment. There was evidence from biological studies to support the potential clinical impact of glucosamine sulphate. For other preparations, the evidence base was less consistent (chondroitin) or absent (glucosamine hydrochloride).

Based on sensitivity analysis and value of information analysis three research priorities were identified:

1. QoL – further clarification of the potential QoL gains [using a generic preference-based QoL measure (such as the Health Utilities Index 3, Short Form-6D, EuroQol-5D) that can readily be used to estimate utility] from treatment with glucosamine sulphate

versus placebo over long-term treatment. Any future trial should also inform our understanding of the relation between QoL and costs of collecting resource use and cost data to allow estimation of the resource impact of any changes in QoL.

2. Structural outcomes – further long-term trial data are required to clarify the impact on the ultimate need for knee arthroplasty, including the ability to delay the need for surgery. As yet, surrogate marks continue to be proposed but, in the absence of long-term follow-up to surgery, the implications of change in surrogate end points remain uncertain.
3. Knee arthroplasty – a nationally representative cohort study is required to understand what proportion of patients with OA (diagnosed in primary care and referred to secondary care) require knee arthroplasty.

Trials of interventions should focus on glucosamine sulphate, and the Rotta product is the only one to date that has demonstrated effectiveness. While uncertainty about other preparations remains, there was insufficient evidence of effectiveness and it was not possible to develop an economic case for further study at this time. Any trial should:

- include collection of information about co-prescribing, the use of other interventions and adverse events
- recruit obese and overweight participants and people across stages of OA severity
- use the opportunity to gather a number of measures of joint structure and damage
- be of at least 3 years' follow-up, with a mechanism to follow the cohort long term (e.g. through record linkage to hospital data).

The biological mechanism of glucosamine sulphate and chondroitin remains uncertain and, in particular, the proposal that the active substance may be sulphate should be explored further.

Chapter I

Introduction

Osteoarthritis (OA) of the knee is a leading cause of pain and disability in the UK. Treatments to date have largely helped only to manage symptoms and have not modified the disease process. While the clinical course of OA is variable, for some the condition progresses to the point where knee arthroplasty is the only option for the management of pain and restoration of function.

Two components of the cartilage structure, glucosamine and chondroitin, are available as food supplements. Proponents of these treatments suggest that oral supplements increase the concentration of these components of cartilage in the joint and may help to preserve, or even repair, the damaged joint in OA.

As food supplements, glucosamine and chondroitin have not been subject to the same rigorous control and licensing processes as medicines. However, one product, a preparation of glucosamine hydrochloride, has received a licence as a prescription-only medicine in the UK. A further glucosamine sulphate product, featured in many of the clinical trials, is licensed in Europe, but not in the UK. A number of randomised controlled trials (RCTs) have been conducted to assess the effectiveness of these treatments in the management of OA and several reviews have sought to summarise the clinical effectiveness. While there has been a degree of heterogeneity in the conclusions drawn, in general, the impact on short-term pain and function outcomes has been disappointing. However, if the mechanism of action is one of long-term disease modification, through joint preservation and repair, as has been suggested, short-term studies may not have been able to demonstrate benefit.

This review sought evidence of the clinical effectiveness of glucosamine and chondroitin in modifying disease progression by focusing on trials of at least 12 months' duration. Disease progression was defined in terms of pain, function, joint structural change and arthroplasty. Economic analysis examined the cost-effectiveness of the addition of these treatments to current care and, using value of information analysis, sought to identify where additional research might most effectively be targeted. A review of biological studies has been included to explore the biological plausibility of a mechanism of action for glucosamine and chondroitin in joint preservation and repair.

Aims and objectives

The aim of this systematic review and economic analysis was to assess the clinical effectiveness and cost-effectiveness of glucosamine sulphate or hydrochloride and chondroitin sulphate in modifying the progression of OA of the knee.

In particular, we sought to address the following questions:

- Do glucosamine and/or chondroitin prevent or slow progression of OA of the knee?
- Is treatment with glucosamine and/or chondroitin safe?
- Is the addition of glucosamine and/or chondroitin to current clinical practice cost-effective?
- Where could research most effectively be focused to address remaining uncertainties?

Chapter 2

Background

Osteoarthritis of the knee: an overview

Osteoarthritis is the most prevalent joint disorder and cause of disability in the UK.¹ Although the incidence increases with age, its onset is not inevitable. Most commonly, OA affects the knees, hips and small joints of the hands. The focus of this review is on OA of the knee and the information presented below, while often applicable to OA at other anatomical sites, will concentrate on the knee joint.

Although there are different systems with which OA is classified, OA can be broadly separated into primary and secondary OA. Primary, idiopathic, OA is the most common. Secondary OA results from previous trauma, infection or congenital abnormality.²

Clinically, OA leads to asymmetric joint swelling, joint crepitus, decreased range of movement and occasionally joint locking. Symptomatically, patients may complain of joint pain with associated short-lived early morning stiffness; however, the degree of severity of symptoms is hugely variable and does not necessarily represent radiological change.

Definition of osteoarthritis

Osteoarthritis has been defined as a chronic disorder characterised by:³

- focal erosive lesions
- cartilage destruction
- subchondral sclerosis
- cyst formation
- large osteophytes at the margins of the joint.

A member of the non-inflammatory arthritides, OA has been described as a degenerative process.² However, there is evidence of an inflammatory response with upregulation of various pro-inflammatory mediators. Recent National Institute for Health and Clinical Excellence (NICE) guidelines for the management of OA highlighted the dynamic nature of the joint remodelling process, describing it as a 'repair

process' for synovial joints. Clinically, a dynamic process is in keeping with the range in severity of symptoms and signs experienced by individuals. In the long term, OA may lead to pain, deformity, impairment of function and, in some patients, a need for knee arthroplasty. For a proportion of patients, symptoms are reported to stabilise or even improve.¹

Diagnosis

The diagnosis of OA is based on clinical examination of the joint and first-line investigation by means of X-ray assessment. Classically, radiographic evidence of OA includes:

- decreased joint space
- osteophytosis
- formation of subchondral cysts
- subchondral sclerosis.

The widely used American College of Rheumatology (ACR) definition of OA is based on a set of clinical criteria along with evidence, from blood tests, of an absence of a primary inflammatory process (*Box 1*).⁴

The recently published NICE guideline for OA¹ simplifies the definition of OA to:

- persistent joint pain that is worse with use
- age 45 years and over
- morning stiffness lasting no more than half an hour

as the basis for a clinical working diagnosis. In the majority of patients, further investigation was felt not to be warranted in routine practice.

Aetiology

The aetiology of OA remains unclear, but it is certainly multifactorial. There is a marked genetic predisposition to the disease with high levels of concordance noted in twin studies. Other factors which come into play include joint shape, occupation and leisure activities. At the cellular level, there is an imbalance of the continuous

BOX 1 American College of Rheumatology definition of OA

A diagnosis of OA of the knee is defined as presenting with pain, and meeting at least five of the following criteria:

- patient older than 50 years of age
- less than 30 minutes of morning stiffness
- crepitus (noisy, grating sound) on active motion
- bony tenderness
- bony enlargement
- no palpable warmth of synovium
- erythrocyte sedimentation rate (ESR) < 40 mm/hour
- rheumatoid factor < 1:40
- non-inflammatory synovial fluid

catabolic and anabolic metabolism, favouring catabolic degeneration of articular cartilage.

Osteoarthritis is the clinical and pathological outcome of a range of disorders that results in structural and functional failure of synovial joints. Osteoarthritis occurs when the dynamic equilibrium between the breakdown and repair of joint tissues is overwhelmed.⁵

In early OA, fibrillation is seen on the surface layer of articular cartilage. This fibrillation tends to correspond to areas of weight bearing and, on microscopy, has the appearance of superficial clefts. As the disease process worsens, these clefts become deeper and this is associated with progressive cartilage loss. Ultimately, the weight-bearing surface of cartilage is destroyed completely, leaving an area of particularly dense subchondral bone. These progressive changes lead to gradual reduction in joint space and ultimately abolition of joint space with 'bone on bone' contact which is visible on standard X-rays.⁵

Risk factors and predictors of disease

A variety of risk factors for developing OA have been identified. These have been classified as:¹

- genetic – it has been estimated that genetic factors account for 40–60% of hand, knee and hip OA
- constitutional (e.g. ageing, female gender, obesity, high bone density)
- biomechanical (e.g. joint injury, occupational and recreational issues, reduced muscle strength).

It appears that there may be different risk factors for disease progression and development.⁶ For example, high bone density has been identified as a risk factor for development, whereas low bone density has been identified as a risk factor for progression in knee OA.⁶ Other risk factors associated with the progression of knee OA include: obesity, low intake of vitamins C and D, and varus/valgus malalignment.^{6–9} Deprivation and manual occupations have also been associated with higher prevalence of knee pain and the need for knee arthroplasty.^{10,11}

Burden of OA

Epidemiology

The epidemiology of OA has been described as 'difficult to determine'.¹ This reflects differences between studies with respect to the method used for diagnosing OA – radiological or clinical.¹² However, even comparing the results of studies using the same broad methodology can be difficult.¹³ For example, a variety of radiological diagnostic criteria are available, and the results may be dependent on which criteria are used.¹³ Furthermore, OA (whether radiologically or clinically diagnosed) will present with varying degrees of severity. Whether or not patients with all degrees of severity are included in prevalence estimates, or only those people with the most severe arthritis, will affect the results.¹³ In addition, radiological and clinical diagnoses do not always correlate.^{7,13} For example, patients with radiological OA of the knee may not experience pain.¹⁴ Similarly, patients experiencing knee pain may not have any radiographic signs.^{9,12}

There also appear to be differences between prevalence rates reported by studies undertaken within different populations.¹⁵ However, due to the methodological issues described above, further studies are required to clarify if these differences

are genuine or an artefact resulting from the method of case ascertainment.¹⁵

Table 1 summarises estimates of the prevalence of knee OA drawn from several studies. While

TABLE 1 Prevalence of knee osteoarthritis contained within the published literature

Reference	Population	Criteria	Prevalence
National Collaborating Centre for Chronic Conditions 2008 ¹	UK Adults aged over 50 years	Radiological	25%
Garstang and Stitik 2006 ¹²	Various countries Adults aged over 55 years	Radiological	At least 33% (and up to 68% in some studies)
D'Ambrosia 2005 ¹³	USA; Framingham study Adults aged 80 years and over	Radiological – severe (grade III or IV)	Women: 21.1% Men: 17.4%
Arden and Nevitt 2006 ⁷	USA Adults aged 75 years and over	Radiological	30%
Corti and Rigon 2003 ¹⁵	Sweden Adults aged 75 years and over	Radiological	Women: 45% Men: 33%
	Netherlands Adults aged 65–75 years	Radiological	Women: 35% Men: 21%
	Italy Adults aged 65 years	Clinical	Women: 26% Men: 12%
Bedson <i>et al.</i> 2007 ¹⁶	UK Adults over 50 years	Clinical	25–37%
Dillon <i>et al.</i> 2006 ¹⁰	USA; National Health and Nutrition Examination Survey (1991–4) Adults aged 60 years and over	Radiological – severe (grade III or IV)	Women: 12.9% Men: 6.5%
White 2006 ¹⁷	Population surveys conducted in the UK among adults aged over 55 years	Knee pain lasting more than 4 weeks	~ 25%
	Adults aged over 60 years	Clinical	10–15%
Williams and Spector 2006 ¹⁸	USA; National Health and Nutrition Examination Survey (1971–5) Adults aged 65–74 years	Radiological – severe (grade III or IV)	Women: 6.6% Men: 2.0%
	UK Adults aged over 55 years	Clinical	18.1%
Brooks 2002 ¹⁹	Spain Adults (no age range specified)	Clinical (self-completed postal questionnaire)	10.2%

The prevalence estimates are contained within review articles which cite primary studies.

not intended to be a comprehensive list, it demonstrates the range of estimates reported within the published literature.

Despite the methodological issues alluded to, some broad conclusions can be drawn. Osteoarthritis of the knee becomes more common with increasing age. In addition, prevalence rates among elderly women exceed those of elderly men.¹³

Natural history of OA of the knee

The natural history of OA is not fully understood.¹⁸ However, in contrast to the widely held view that OA is an invariably progressive, deteriorating condition, it would appear that the condition can remain stable for some time.⁷ While radiographic recovery is uncommon, radiographic signs may stabilise and clinical outcomes may even improve. This is reflected in the relatively low proportion of patients coming to surgery and has been reported even among patients referred to specialist clinics.²⁰

A recently published guideline on the management of OA states that, over a period of several years, approximately one-third of patients with knee OA improve, one-third remain stable and one-third deteriorate.¹

Several authors^{17,20,21} have reported that the clinical progression of OA is variable. Some patients may experience rapidly progressive disease, while in others, the condition can remain stable for many years. White¹⁷ described a study which found that up to 40% of patients with significant radiographic knee OA showed no deterioration when repeat radiographs were performed 20 years later. It has been claimed that when followed up for over a decade, radiographic signs of joint degeneration did not progress in one-third to two-thirds of patients with OA of the knee or hip.²¹ In one small study that followed up 63 patients with knee OA over an 11-year period, the radiographic appearance improved in 10% of patients.²¹ Dieppe and colleagues²⁰ followed up over a 3-year period approximately 400 patients with OA who had been referred to a specialist rheumatology clinic. Two-thirds of the patients recruited had OA of the knee. Fifty-eight per cent of patients reported an overall worsening of their condition. Twenty-one per cent reported no change and 21% reported an overall improvement. With respect to pain, there was considerable individual patient variation with many patients reporting markedly different levels of pain at follow-up compared with baseline. All measures of function showed an overall deterioration.

Dieppe and colleagues²⁰ found that there was no correlation between radiographic change and clinical outcomes. They suggested that X-ray appearances may poorly reflect morphological changes within joints, or alternatively that clinical and radiographic changes are out of step with each other. Johnson and colleagues²² explored the association between self-assessed symptoms and functional and radiological measures, reporting a poor correlation after 7 years. Improvements in self-assessed symptoms (in 25% of participants) were not reflected in measures of function or on imaging. The authors raise the question of the role of adaptation by patients as they develop strategies to avoid pain. Assessments focusing on pain or ability to complete certain tasks will not detect the more subtle changes in social and physical activity that may be occurring as a coping mechanism.²²

Consequences for health

The pain and disability associated with OA can have a marked effect on patients' quality of life (QoL) and their ability to live independently.¹⁷ People with the condition can experience significant limitations with respect to undertaking activities of daily living.¹⁴ OA of the large, weight-bearing joints (hips and knees) is particularly debilitating,^{7,15} and it has been claimed that knee OA is the most frequently reported cause of disability in older adults.²³ Disability in relation to walking and using stairs that is attributable to knee OA equals that associated with cardiovascular disease.¹⁵ A number of chronic conditions (e.g. hypertension, diabetes mellitus) may contribute to disability. If present, such conditions may add to the difficulties experienced by patients as a consequence of their arthritis.¹⁵

Hawker and colleagues²⁴ conducted a study to explore the nature of the pain experienced by people with knee and hip OA. Ninety-one of the 143 participants recruited had knee OA. Two main types of pain were described: a constant dull, aching pain and an intermittent, unpredictable, intense pain. The latter was associated with the avoidance of social and recreational activities, as well having an adverse effect on the patients' mood.

Other studies have reported a high prevalence of psychological morbidity among patients with knee OA.^{23,25} As well as affecting patients' QoL, this may also impact on their use of health services. Rosemann and colleagues²⁶ report that depression was positively associated with patients consulting

their GP and being referred to an orthopaedic specialist because of knee pain, although other studies have reported an inverse relationship.¹⁶ However, both situations are problematic. It may be the case that some patients referred to an orthopaedic specialist are undergoing surgery when, in the first instance, treating their depression would have been more appropriate. It is also possible that depressed patients who do not engage with health services are missing out on care from which they would benefit.

Several studies have reported that patients with knee pain may not consult health professionals.^{16,27} A variety of contributory factors have been proposed. It has been suggested that patients view knee OA pain as being an inevitable consequence of ageing and something which has to be tolerated.²⁷ It has been suggested that the attitude of health professionals can contribute to this (e.g. by discussing knee pain and OA using terms such as 'wear and tear').²⁷ Studies also suggest that some patients have a degree of therapeutic nihilism and believe that little can be done to alleviate their pain.²⁷ Other studies suggest that some patients fear becoming addicted to analgesics or experiencing medication side effects.²⁷

Current standard care/optimal care

Treatment

A range of treatments can help to manage the symptoms of OA of the knee. Non-pharmacological interventions include weight loss, exercise and a range of physiotherapy interventions. Pain control is achieved through the use of exercise, simple analgesia, non-steroidal anti-inflammatory drugs (NSAIDs) and, if necessary, opiates. Transcutaneous electrical nerve stimulation (TENS) machines, heat therapy and topical NSAIDs may also be used. If non-invasive interventions fail to control symptoms, then intra-articular injections, arthroscopic lavage and debridement for joint locking, and ultimately arthroplasty have been utilised with evidence of varying degrees of effectiveness. The primary aim of these treatments is management of symptoms, in particular pain and loss of function. Most of these treatments do not modify disease progression.²

Management of OA of the knee

In the UK, information about current health-care practice in the management of OA of the knee is scarce.²⁸ While we may not have clear

details of current practice, a guideline produced by NICE in 2008,²⁹ and based on work by the National Collaborating Centre for Chronic Conditions (NCCCC),¹ provides recommendations for the care pathway for people with OA. *Figure 1* summarises the recommended care. The three core treatments in the centre circle were recommended for all patients. Paracetamol and topical NSAIDs were recommended as the first line in analgesia; treatments in the outer circle then being recommended for only selected individuals. The guideline authors did, however, note a number of areas of uncertainty including: the most effective combinations of treatments; how to improve adherence to the non-pharmacological interventions; and how most effectively to treat very elderly patients.

Current care

Non-pharmacological interventions

There are no national data about the levels of current practice in relation to the non-pharmacological interventions outlined in the centre circle. If guideline uptake was complete then all patients with OA would receive these core treatments. The guideline does not estimate the cost or service implications of implementing these changes. Chevalier and colleagues³⁰ conducted a questionnaire survey among French general practitioners to investigate the management and treatment of knee OA. They compared the survey results with recommendations produced by the European League Against Rheumatism in 2000 and found that non-pharmaceutical treatments, including recommencing exercise and weight loss as first-line approaches, appeared to be underutilised. They reported a high request rate for radiological examinations even if not required; the underutilisation of non-pharmacological treatments as a first-line approach; the inappropriate use of bed rest; and high use of oral NSAIDs as a first-line analgesic.

Pharmacological interventions

The main changes to practice identified in the NICE guideline²⁹ are around the use of paracetamol and topical NSAIDs as first-line care. This change in practice, if implemented, was identified as critical in reducing the adverse events experienced in relation to the use of NSAIDs. Approximately 167,000 people with OA in England (based on a sample of primary care practices) were estimated to be treated currently with topical NSAIDs, increasing to more than 2.5 million if the guideline was adopted (a total

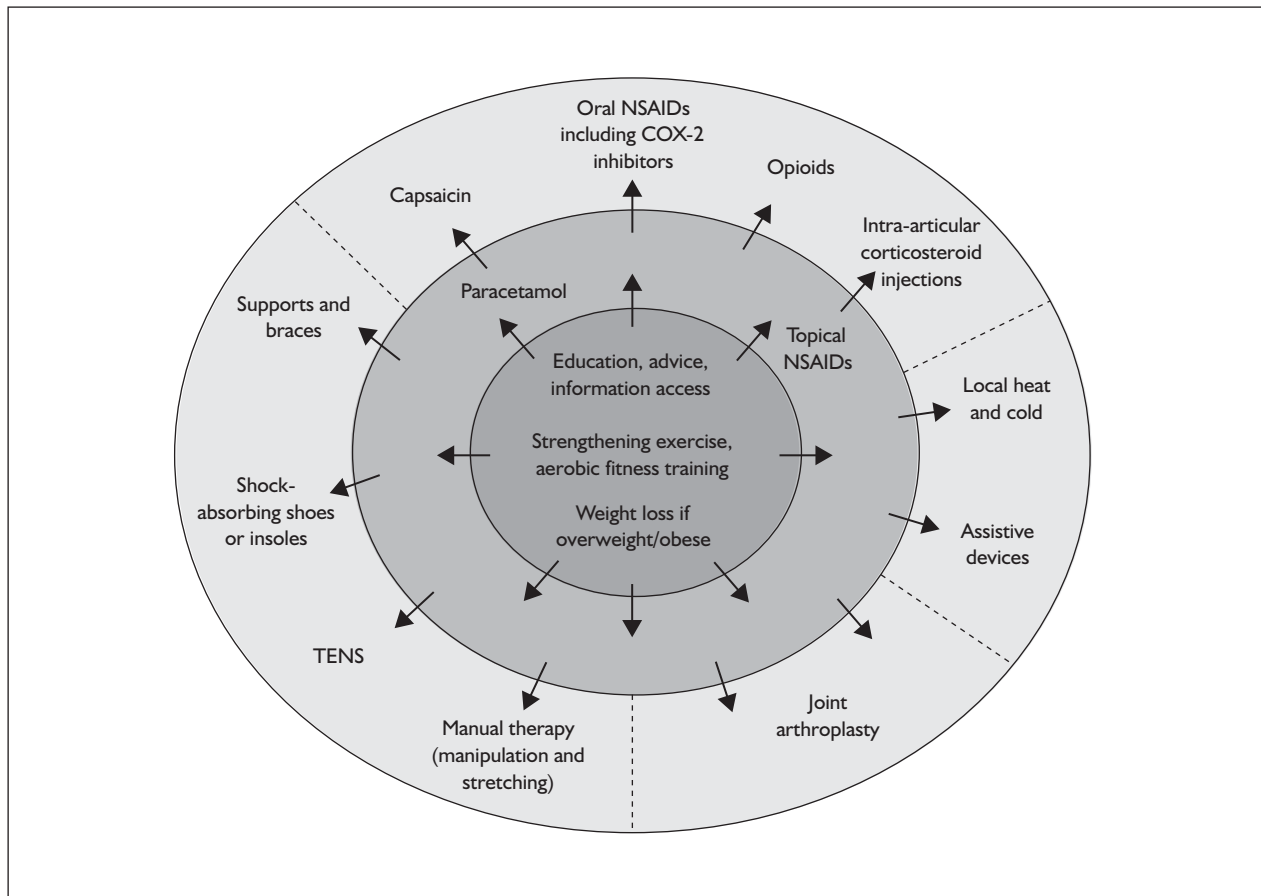


FIGURE 1 Targeting treatment: a summary of the treatments recommended. COX-2, cyclo-oxygenase-2; NSAIDs, non-steroidal anti-inflammatory drugs; TENS, transcutaneous electrical nerve stimulation. (Reproduced from: National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults. London: Royal College of Physicians, 2008. Copyright © 2008 Royal College of Physicians. Reproduced by permission.)

cost of approximately £17million per year). Data about oral NSAID and cyclo-oxygenase-2 (COX-2) inhibitor utilisation were limited, and based on clinical judgement, with an estimated 50% of people with OA receiving these treatments. The other main change in practice would come from the dual prescription of proton pump inhibitors to all patients receiving NSAIDs or COX-2 inhibitors, but again estimates about current practice were not based on collected data. These data applied to OA as a whole, i.e. were not restricted to OA of the knee.

Intra-articular injections with hyaluronic acid were not recommended for use. No data were presented on the extent of use in current practice.

Invasive procedures

Two main invasive procedures are used in the management of OA of the knee:

- arthroscopic lavage and debridement
- knee arthroplasty.

Hospital Episode Statistics (HES) data in 2005–6 reported that 19,686 people over the age of 45 years received arthroscopic lavage and debridement in England. One of the major conclusions of the NICE guidelines for OA was to recommend that this procedure only be used where patients have a clear history of mechanical locking. The guideline predicts that following this guidance would result in one-third fewer patients receiving arthroscopies.

Audit data from England and Wales, complete for more than 85% of National Health Service (NHS) hospitals, reported that 57,597 knee arthroplasties were conducted in 2006; of these 97% were for OA. The average age of patients undergoing surgery was 70 years and 57% were female.³¹

Economic burden of OA

It has been estimated that OA in general costs the US economy \$60–65 billion annually.^{12,21} In the UK during the period 1999–2000, an estimated

36 million working days were lost as a result of OA, with a cost of £3.2 billion in associated lost productivity.¹

Osteoarthritis has major impacts on health services. It is estimated that two million adults attend their GP each year as a consequence of OA.¹ With respect to knee pain, the incidence of new GP consultations among those aged 50 years and older is estimated at 10% per annum.¹ As noted above, in the order of 58,000 primary knee arthroplasty operations are carried out annually in England and Wales for OA of the knee.

A UK population survey conducted by Yong and colleagues¹¹ attempted to estimate the proportion of the population aged 65 years and older that may benefit from knee arthroplasty based on Lequesne index scores. It was reported that 7.9% of respondents were assessed as possibly requiring knee arthroplasty. This dropped to 5.1% once patients with specified contraindications to surgery were taken into account. Of these patients, 5.3% appeared to be candidates for bilateral knee arthroplasty.

A trial of patient education for management of OA of the knee conducted in the UK in 1996–7, and including an economic evaluation, provided a detailed and valuable source of costs of care at that time.³² The estimated direct cost of knee OA-related health care over the 2-year study period (excluding the trial intervention) was £212 per patient for the NHS. Within this total, medication and primary care costs were estimated to be, on average, £50 per patient. The mean hospital-based costs per patient were £52 (including radiology) with a further £20 for allied medical professions and complementary therapists on the NHS. Patients paid £78 per patient for private consultations with allied health-care professionals (largely physiotherapy), complementary therapy, travel expenses, prescription charges and over-the-counter medicines. The cost for society as a whole was £291 per patient.³²

With a mean study population age of 65 years, the trial participants may have been a little younger than the general population of people with OA of the knee. Seventy-one per cent were female and 55% of participants had at least 3 years of OA history prior to recruitment. Approximately 15% of patients required a hospital inpatient stay during the 1-year follow-up period, accruing a total of 5.9 days as inpatients in orthopaedics. For the 170 patients in the study, 276 visits to the GP were

required in the 12 months prior to the trial and 52 outpatient clinic appointments were necessary for management of their OA.^{32,33}

Studying OA treatments in trials

Studying the impact of treatments on OA within trials has been challenging. Progression of disease occurs over years and decades. The number of people deteriorating to need arthroplasty is relatively small in relation to the total population with knee OA. Thus, studying interventions that aim to modify the course of the condition requires either very long follow-up or a surrogate marker for progression.

Surrogate end points for trials are often criticised. In knee OA, two main types of end points have been adopted in trials of interventions: composite scoring systems for pain and function specific to OA; and measures of joint space.

Measures of health state in OA

Standard generic measures of QoL such as the 36-item Short Form General Health Survey (SF-36) have not been widely adopted in trials of therapy for knee OA. Several instruments are available for assessing pain and function specifically in OA. Lequesne³⁴ developed a scoring system for severity of knee OA based on pain, walking distance and activities of daily living, and using this, subdivided patients into levels of severity of disability. The Western Ontario and McMaster Universities OA index (WOMAC)³⁵ is another index for the assessment of OA of the knee or hip and is based on assessment of pain, stiffness and physical function. The WOMAC index is probably the most widely used within trials.^{35–37} It has been rated as the leading tool in OA of the knee and hip; however, problems have been identified where function and pain domains are divergent in terms of a patient's experience.³⁸ The most commonly used tools are summarised in *Table 2*.

Trials generally present a mean treatment group difference from baseline to the end of the trial. In order to interpret the difference there is a need to understand the clinical significance of the change, sometimes known as the 'minimal clinically important difference' (MCID). The MCID is a threshold and how such cut-off points are defined is not standardised and is vulnerable to the approach used. They do, however, give an

TABLE 2 Summary of composite health status scales commonly used in trials of treatment for OA

Scoring system	No. of questions	Scale	Scale details	Pain	Function	Walk distance	Stiffness	Mental Health	OA Specific	Knee Specific	Validated in OA
Oxford Knee Score	12	5–60	Each question scores 1–5. 60 is worst score	Yes	Yes	Yes	No	No	Yes	Yes	Yes
SF-36	36	0–100	0 is bad, 100 is good. Scores are broken down into eight subcategories	Yes	Yes	Yes	No	Yes	No	No	Yes
WOMAC	24	Uses VAS 100 mm scale or Likert 0–5	Scores are broken down into 0–20 (pain), 0–8 (stiffness), 0–68 (physical function)	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Lequesne	10	1–24	Combined severity score, 1–4 mild OA; 5–7 moderate; 8–10 severe; 11–13 very severe; > 13 extremely severe	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
VAS, visual analogue scale.											

idea of the magnitude of effect needed for patients to express an improvement in their clinical state. Tubach and colleagues³⁹ estimated the MCID using WOMAC and a 0–100 scale in patients with knee OA, stratifying by baseline symptom severity. The MCID for patients with low baseline scores was estimated to be a 5-point improvement [95% CI (confidence interval) 4 to 7]. For those who reported intermediate baseline scores, a 12-point (95% CI 10 to 15) improvement was considered clinically important. For those with high baseline scores, the MCID was 20 (95% CI 18 to 23).³⁹

None of these patient QoL scoring systems are in use in clinical practice outwith the context of a trial, and they have not been designed for individual patient clinical decision-making. A working group from OMERACT (Outcome Measurement in Clinical Trials) and OARSI (Osteoarthritis Research Society International) has been working on new definitions of severity of knee and hip OA, with a view to considering when knee arthroplasty is necessary.⁴⁰

Measuring joint space width

Osteoarthritis has typically been considered a slowly progressive condition; however, in OA of the knee, the outcome is variable. While radiographic recovery is uncommon, it can occur, as mentioned above.²¹ Clinical outcomes, measured using the scales described above, may stabilise or improve. So, while clinical care of OA is based on clinical symptoms, there has been substantial research interest in assessing if interventions are modifying the long-term disease process, reducing joint damage and, ultimately, reducing the progression of symptoms and the need for knee arthroplasty or other surgical interventions.

Markers for those at risk of progressive disease have been sought. Radiological markers of joint damage, in particular joint space narrowing, have been widely accepted as surrogate markers for structural damage and have been recommended as a primary end point for clinical trials by scientific organisations and regulatory agencies in Europe and the USA.⁴¹

Some studies use tools such as the Kellgren–Lawrence scale based on radiological appearances:

- Grade 0 Normal
- Grade 1 Questionable: doubtful narrowing of joint space and possible osteophytic lipping

- Grade 2 Mild: definite osteophytes and possible narrowing of joint space
- Grade 3 Moderate: moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends
- Grade 4 Severe: large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

The use of scales is subjective and, in the context of clinical trials and assessing disease progression over time, may lack reproducibility. With only five grades, such tools are relatively crude and subtle changes cannot be represented. Joint space has the advantage that it can be measured using standard X-rays. The relationship between joint space, progressive joint damage and progressive symptoms is discussed below.

Definitions of joint space in the knee

Healthy knee

In a healthy knee joint, articular cartilage, not normally visible on standard X-rays, fills the joint creating an apparent space on X-rays between the visible femoral and tibial bones. The knee joint space can be summarised by a number of measures on standard X-rays; the commonly used measures are summarised below:

- mean medial joint space
- minimum joint space
- mean lateral joint space
- minimum lateral joint space.

Joint space loss is a characteristic radiological feature of OA, as well as rheumatoid arthritis and other inflammatory arthropathies. In these conditions, joint space loss represents loss of articular cartilage.⁴² What constitutes a ‘normal’ healthy joint space on standard X-ray is not well studied. X-ray studies among people attending Accident and Emergency (A&E) for investigation of knee pain or following minor trauma, and considered ‘normal’ by a radiologist, have reported on joint space. In this population, there was little difference between weight bearing and non-weight bearing imaging; a finding believed to reflect the relative lack of ligament laxity in the normal knee.⁴² Joint space in the healthy knee is consistently reported to be less in women than in

men. Dacre and colleagues⁴² reported that medial and lateral joint spaces decreased with age, but were not associated with body mass index (BMI), height or weight. *Table 3* summarises measures of normal joint space.⁴²

Osteoarthritic knee

In OA of the knee, joint space volume varies among individuals. A number of approaches to systematically describing the changes seen on X-ray in OA of the knee have been reported. Several grading systems have been used and these can be split into two types:

1. Semi-quantitative – defining the grade of joint damage based on joint space loss, osteophyte formation, subchondral sclerosis, angular deformity and cyst formation. Various scoring systems have been reported since the original scale by Kellgren and Lawrence and accepted by the World Health Organization (WHO).^{43,44}
2. Quantitative – with formal measuring (chondrometry) joint features. Again, various methods have been applied to how and where to measure.⁴⁴

Single baseline measure as a predictor of severity of symptoms or progression

Joint space width at baseline was reported as a predictor of complete joint space loss (score = 3 on a scale of 0–3) in a long follow-up study in the USA,⁴⁵ with 50% of patients with a baseline joint space width score of 1 progressing to complete joint space loss in 12.03 years, and in 7.44 years if baseline joint space width score = 2.

A number of studies have reported little correlation between baseline (one point in time) measures of joint space width (mean or minimum) and symptoms of OA (pain, function or composite measures such as WOMAC score).^{46–49} Comparisons of joint space width with direct arthroscopy visualisation of the joint space also report poor sensitivity and specificity.⁵⁰

Change in joint space width as a predictor of symptoms

Joint space narrowing over 2–3 years has been reported by some authors, to correlate with baseline pain scores and changes in measures of pain,^{47,51} but has not been a consistent finding by all.²⁰

Bingham and colleagues⁵¹ reported that a 60% joint space narrowing in 2 years correlated with a 10 mm increase in pain, function and total WOMAC scores using a 100 mm visual analogue scale (VAS).

Change in joint space width as a predictor of joint damage progression

A correlation between joint space narrowing and knee arthroplasty has been reported, with a minimum medial joint space narrowing > 0.5 mm over 3 years being a predictor of knee arthroplasty [relative risk (RR) 3.5, 95% CI 1.23 to 9.97] in the subsequent 5 years, but was based on small numbers of patients progressing to knee arthroplasty.⁵² Minimum medial joint space narrowing of > 0.6 mm in 3 years gave an RR of 5.16 (95% CI 1.76 to 15.12) of surgery.⁵³

Ciccitini and colleagues⁵⁴ reported that joint space loss, as measured by magnetic resonance imaging (MRI), correlated with knee arthroplasty. Of the 37 people with a rate of loss of < 3% (based on MRI at year 0 and year 2), three required knee arthroplasty by 4 years. In comparison, for the 36 with a tibial cartilage loss of > 8% per year, eight needed knee arthroplasty; an RR of 7.1 (95% CI 1.4 to 36.5) after adjustment for factors such as age, gender, BMI, etc.⁵⁴

Issues with measuring knee joint spaces

Reproducibility of procedure for X-ray

In the diseased knee, the positioning during imaging is important, with substantial differences

TABLE 3 Summary of measures of normal joint space

Dacre 1991 ⁴²	Male	Female
Mean medial joint space (mm)	7.03 (6.91–7.15)	5.73 (5.58–5.88)
Mean lateral joint space (mm)	7.44 (7.30–7.58)	6.44 (6.30–6.58)

in joint space measurements depending on weight bearing and position. The OARSI issued a protocol for imaging the knee in guidelines published in 1996, recommending:

A standing (weight bearing) antero-posterior fully extended knee view.⁵⁵

Since then various modifications have been tried. Variations in method do affect the absolute measures and require the position to be reproduced in order to minimise within-study comparisons or assessment of change over time.^{56–58} Protocols must also set out the imaging technical details if reproducibility over time is to be achieved, i.e. focus to film distance, radiological parameters and control for joint rotation.⁵⁹

Reproducibility of measurements

Intraobserver reproducibility for joint space measurements has been reported to be high [$k > 0.88$;⁴⁹ $k = 0.77$ (0.72–0.82)].⁴³ Inter-observer reproducibility was lower (lateral $k = 0.6$; medial $k = 0.72$).^{43,49} Grading joint space loss based on a scale and using comparative images as examples improved intra- and inter-observer reproducibility.⁶⁰ The use of automated systems to measure joint space width from digital images is likely to reduce this source of error and has been widely adopted in trials.

Impact of pain on positioning of the knee

Knee pain has a major impact on a person's ability to fully straighten (extend) their knee joint. The degree to which extension is achieved may, therefore, be modified by treatments that modify pain. As a result, the joint space width would be artificially altered, reflecting not the cartilage volume, but rather the degree of extension achieved. This is a potential confounder in trials.⁵⁹

Assessment of knee OA progression in clinical trials

Western Ontario and McMaster Universities osteoarthritis index scores and measures of joint space change have been adopted by OMERACT and regulatory bodies as the key outcome measures for clinical trials in knee OA.^{40,59} Despite the various caveats outlined above, these measures have been widely adopted by trialists. Few studies have achieved long-term follow-up of trial participants to measure other hard clinical end points, such as knee arthroplasty.

Relation to clinical practice

While patients are often assessed using X-rays in clinical practice, pain is the major feature that determines when further intervention is required. The correlation between radiological changes and symptoms, as has been noted, is poor. X-rays are used widely in trials to assess disease progression, but this does not translate into clinical decision-making about when surgery is required.

Interventions under investigation

Glucosamine and chondroitin

Both glucosamine and chondroitin are natural constituents of hyaline cartilage. With the exception of one preparation of glucosamine, in the UK they are considered, for regulatory purposes, to be food supplements. It has been claimed that glucosamine and chondroitin reduce the pain of OA, but recent systematic reviews have cast doubt on this.^{61,62} However, it has also been suggested that glucosamine might have some effect on preserving cartilage in early OA, and hence might slow down progression.

As a food supplement, glucosamine and chondroitin can be bought by anyone, either over the counter or by mail order, without the need for a prescription. They come in different forms and doses, and may be taken on their own or mixed with food and drink. For example, glucosamine may be added to a range of drinks, from iced tea to fruit smoothies.

Glucosamine

Glucosamine is a naturally occurring amino sugar that is a building block for the complex proteins called glycosaminoglycans which are part of the structure of cartilage. Hyaline cartilage is composed of about 50% collagen, and the remainder is mainly made up of proteoglycan molecules which serve to give the cartilage a viscoelastic resilience and thus to act as a cushion. The proteoglycan molecules (also called aggrecans) consist of numerous long-chain glycosaminoglycans linked to a core protein. The glycosaminoglycans are repeating disaccharide units consisting of a hexuronic acid and a hexosamine (amino sugar). Glucosamine ($C_6H_{13}NO_5$) is the hexosamine constituent of keratan sulphate, which is found in hyaline cartilage alongside the glycosaminoglycans chondroitin 4-sulphate and chondroitin 6-sulphate (which are therefore much larger molecules than glucosamine).⁶³

Two forms of glucosamine exist for use as oral supplements: glucosamine sulphate and glucosamine hydrochloride. Glucosamine is usually derived from shellfish (chitin); however, it may also be obtained from the chitin present in the cell walls of many fungi (which may be of advantage for people with shellfish allergy).⁶⁴ Oral (either in tablet form or as a powder dissolved in water), intramuscular and even intra-articular preparations exist. Doses vary considerably between and within preparations. Commonly used dosages are between 1250 mg and 1500 mg daily.

Chondroitin

Chondroitin is a large gel-forming molecule, which forms part of cartilage and confers resistance to compression. Despite being a large molecule, it is partially absorbed from the diet or supplements.

Chondroitin is used orally as chondroitin 4- and 6-sulphate. It is made from extracts of cartilaginous cow and pig tissues (tracheal cartilage), or from fish or bird cartilage.² Chondroitin is usually taken orally, either in tablet form or as a powder dissolved in water, but intramuscular applications have also been used. Commonly used dosages are between 800 mg and 1200 mg daily, but again can vary substantially between and within products.

As regards the possible mechanism of action by which glucosamine and chondroitin might work in OA, the hypothesis is that oral supplements of these compounds taken on their own or in combination may help strengthen or repair cartilage, thus having disease-modifying potential in OA. We address in detail the biological plausibility of glucosamine and chondroitin as a disease-modifying agent in OA in Chapter 5.

Glucosamine and chondroitin availability in the UK

Licensed preparations

In 2007, Alateris[®] (Ransom, UK) (glucosamine hydrochloride) was licensed in the European Union and made available as a 'prescription only medicine' in the UK. There were no clinical trials for this product to support the licensing application. The tablets are 625 mg and the recommended dosing is two tablets (1250 mg) per day. A 1-month supply was priced at £18.40 in the *British National Formulary* (BNF) in May 2008. As a new product, Alateris is monitored under the UK Department of Health, Medicines and Healthcare Products Regulatory Agency (MHRA) 'black triangle' intensive surveillance scheme.⁶⁵

The only other 'prescription only medicine' glucosamine product (glucosamine sulphate), produced by Rotta, Italy, with a medicinal licence in some European countries is not currently available in the UK. It is used at a dose of 1500 mg per day.

Food supplements

Glucosamine, chondroitin and combination products are also available in the UK as non-licensed food supplements from health food shops, pharmacies and the internet. Food supplements are not subject to the same rigorous testing and control measures as licensed medicines and the products may vary in relation to combinations, compounds, strengths and purities.

Adebowale and colleagues⁶⁶ studied 14 products containing glucosamine sulphate or hydrochloride and 11 products containing chondroitin sulphate available on the US market. Deviations from label claims for glucosamine content ranged from as low as 25% to over 115% (although only two products appeared to contain less than 90% of the label claim). For chondroitin sulphate, deviations from the label claim ranged from less than 10% to 110%, with 4 of 11 products containing less than 40% of the claimed chondroitin content. A further testing of 32 chondroitin sulphate products, using a phototrode titration method, found that over half of the products contained less than 40% of the label claim (with all of the products costing less than US\$1 containing less than 10%). Barnhill and colleagues⁶⁷ tested 20 chondroitin sulphate products available in the US and found that none complied with the Food and Drug Administration (FDA) good manufacturing practices for pharmaceuticals. *Table 4* provides an illustration of the costs associated with different preparations.

Prescribing glucosamine and chondroitin

Alateris (glucosamine hydrochloride) appears in the BNF as the only product licensed as a 'prescription only medicine' available for prescription in the UK. In June 2008, the Scottish Medicines Consortium (SMC) reviewed the suitability of Alateris for use in NHS Scotland in terms of clinical effectiveness and cost-effectiveness and concluded that:

Alateris is not recommended for use within NHS Scotland for relief of symptoms in mild to moderate osteoarthritis of the knee. No direct clinical trial evidence of the efficacy and safety of this specific product is available. Randomised controlled trials of other formulations of glucosamine hydrochloride

TABLE 4 Example prices of preparations in the UK in 2008 (subject to special offers and deals between manufacturers and retailers)

Preparation	Composition	Price
Valupak	30 tablets (400 mg GI + 100 mg Ch)	£0.99
Valupak Joint Care	30 tablets (500 mg GI + 400 mg Ch)	£4.99
Newmark	30 tablets (400 mg GI + 100 mg Ch)	£1.80
Newmark Glucosamine	30 tablets (500 mg GI)	£1.89
Natures Aid Glucosamine	90 tablets (100 mg GI)	£12.00
Alateris	60 tablets (625 mg GI)	£18.40 (BNF 2008)

BNF, *British National Formulary*; Ch, chondroitin; GI, glucosamine.

indicate little or no benefit over placebo in improving symptoms in patients with osteoarthritis of the knee.

In addition, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.⁶⁸

Food supplements, as unlicensed products, are either 'blacklisted' as not for prescription or what is called 'pay and report', i.e. if a prescription is issued, the pharmacist is reimbursed for the script but the prescription is reported to the local health board to follow up.⁶⁹ The scale of use of glucosamine and chondroitin in the UK is not well documented. One small survey in two GP practices in the UK⁷⁰ identified that 16% of people with OA had used glucosamine and 5% had used chondroitin. In Scotland, in 2007, only 376 items for glucosamine hydrochloride were dispensed on prescription (Mr D Pflieger, Robert Gordon University, 2009, personal communication).

Key questions and rationale

Some of the findings in this chapter have implications for the interpretation of the evidence, including the following:

- OA of the knee is diagnosed mostly on clinical grounds.
- Progression is variable; symptoms improve in a significant minority.
- Radiological changes do not usually regress, but often do not progress.
- Clinical symptoms may not correlate with radiological changes.
- Progression is slow, over many years.
- There are tried and tested instruments for assessing the impact of OA, such as WOMAC.

- Joint space is the main objective measure, but there can be some subjectivity in quantifying. The link to long-term outcomes is not well established.

In undertaking this review and economic evaluation, we were aware that a number of reviews had already been published. In general, these had included studies of short duration and had not focused on long-term outcomes. In this report, we were interested in the progression of knee OA and whether glucosamine and/or chondroitin could modify the disease process. We were, therefore, only interested in trials of sufficient duration to assess long-term outcomes. We have restricted our review to studies of a minimum of 12 months' follow-up.

The questions we planned to address in this report are summarised below:

1. Does glucosamine prevent or slow progression of OA of the knee?
2. Does chondroitin prevent or slow progression of OA of the knee?
3. If so, does the combination of both offer any greater effect?
4. If they are useful, what dosages should be used?
5. What are the costs, in terms of both the product costs and any side effects?
6. Are there any savings to the NHS from their use, for example by reduced consumption of prescribed NSAIDs, or from avoidance of knee arthroplasty procedures?
7. Is there evidence of cost-effectiveness from well constructed economic evaluations?

From the evidence review we sought to be able to come to one of three possible conclusions:

1. The evidence base is sufficient to conclude that they are not effective.
2. The evidence base is sufficient to conclude that these products are clinically effective, in which case further research into clinical effectiveness is not required.
3. The evidence is inconclusive, but suggestive enough of benefit to justify further research.

If further research was indicated, then we planned to address several further questions, where the data permitted:

1. Are the alleged benefits of glucosamine and chondroitin on knee cartilage biologically plausible?
2. If, as suggested by the commissioning brief, the evidence suggests that there is no gain in short-term symptom relief, but only in long-

term preservation of cartilage (which does imply longer-term reductions in symptoms, advanced OA and perhaps of the need for knee arthroplasty), what should the comparator in trials be?

3. If the gain is in long-term outcomes, are there short-term indicators of benefit which could be used, rather than waiting 20 years for advanced OA to become manifest?
4. Which variables or assumptions (e.g. costs, QoL, mortality, extrapolation of effectiveness over time) are most important in generating uncertainty in the cost-effectiveness estimates, and which would provide the greatest return in terms of reducing uncertainty at a reasonable cost. These variables and assumptions will be identified using value of information analysis, and will form the main basis in recommendations for further research.

Chapter 3

Clinical effectiveness of glucosamine and chondroitin on the progression of OA of the knee

In this chapter we cover the evidence of clinical effectiveness of glucosamine and chondroitin on the progression of OA over at least 12 months. A number of reviews have been published in recent years. Many of these have included studies of short duration which, while adequate for addressing short-term effects, including the effect on pain and function in the short term, are not adequate for studying whether these treatments have an effect on the natural history and clinical progression of the disease.

Methods

Inclusion criteria

Types of studies

In the first instance, we reviewed systematic reviews of RCTs where the review included at least one trial which met our duration inclusion criteria. The acceptable minimum duration of follow-up was 12 months, i.e. reviews had to include at least one primary study with a study duration and/or duration of follow-up of 12 months.

We then used these reviews as a source to identify RCTs of at least 12 months' duration. We also considered any additional RCTs published after the last search of any relevant included review, or any RCTs not included in any of the reviews, but fulfilling our inclusion criteria.

Types of participants

People with OA of the knee were included. No restrictions were made regarding stage of OA, but information on OA stage was noted as indicated by the reviews.

Types of interventions

Treatments with glucosamine or chondroitin taken in pharmacological form (capsule/tablet or powder) were included (any salts and any doses, with glucosamine and chondroitin being used alone or in combination). Topical applications or injections were excluded. Glucosamine or chondroitin taken as additives to drinks were not included.

Where data permitted, glucosamine sulphate and hydrochloride studies were to be analysed separately. Trials of the Rotta product of the sulphate form were also to be analysed separately.

Recent NICE guidelines reiterate that none of the existing treatments have been demonstrated to modify OA disease progression. The main comparator was therefore placebo, but comparisons with analgesics and non-pharmacological interventions were not excluded. Different comparators would have been explored by sensitivity analysis if appropriate data had been found.

Types of outcome measures

Because this review was prompted by the suggestion that glucosamine and chondroitin might have structural effect, systematic reviews were only considered for inclusion if they assessed both pain/function and a measure of joint structure, such as joint space loss. Randomised controlled trials were considered if they assessed function or structure.

Data on the following outcome measures were extracted:

- pain
- function
- composite measures of health status (WOMAC score, Lequesne index, SF-36 or similar)
- joint space loss (as defined in the trials)
- knee arthroplasty
- adverse events.

Search strategy

The search strategy comprised the following main elements:

- searching of electronic databases
- scrutiny of bibliographies of retrieved papers
- checking for details of registered, but unpublished trials
- internet searches

- the Food Standards Agency website for details on safety.

Electronic databases included: MEDLINE and PubMed; EMBASE; the Cochrane Library (including the Cochrane Systematic Reviews Database, CENTRAL, DARE, NHS EED and HTA databases); Allied and Complementary Medicine (AMED); National Research Register (NRR); Web of Science Proceedings; Current Controlled Trials; and Clinical Trials.gov.

To identify additional recent RCTs that were published after the publication of high quality reviews, searches for RCTs were carried out back to the beginning of 2004 for glucosamine and back to 2005 for chondroitin. A separate search was done to identify studies specifically investigating adverse events of glucosamine and/or chondroitin. See Appendix 1 for details.

We considered only papers published in English, German, French, Italian and/or Spanish. Reports published as meeting abstracts only (with insufficient methodological details reported to allow critical appraisal of study quality) were excluded, except as a guide to trials not yet published in full.

Study selection

Titles and abstracts were examined for inclusion by one reviewer. Full copies were obtained of papers that appeared to fulfil the inclusion criteria (or where there was doubt) and these were checked by two reviewers independently for final inclusion. There were no disagreements.

Quality assessment

Potential systematic reviews were assessed according to the following criteria, which are based on the criteria of the Quality Of Reporting Of Meta-analyses (QUOROM) statement:⁷¹

1. inclusion criteria described (study design, participants, interventions, outcomes)
2. details of literature search given (databases, dates, keywords, restrictions)
3. study selection described
4. data extraction described
5. study quality assessment described
6. study flow shown
7. study characteristics of individual studies described
8. quality of individual studies given
9. results of individual studies shown

10. was the statistical analysis appropriate?

Studies were considered to be systematic reviews if they described inclusion criteria, gave details of their literature searches and fulfilled at least half of criteria 3 to 10. In addition, the reviews had to fulfil the remaining inclusion criteria for our review, i.e. they (i) summarised RCTs, (ii) included at least one RCT of at least 1 year's duration, (iii) included at least one RCT including patients with OA of the knee, (iv) considered the effects of glucosamine sulphate or hydrochloride or chondroitin sulphate, alone or in combination, compared with placebo, and (v) reported data on both symptoms/pain and structure/joint space.

Studies were classified as being high, moderate or poor quality, according to the following criteria:

- high quality: all criteria fulfilled, or not more than one of 'description of study selection' or 'description of study flow' not fulfilled
- moderate quality: more than one of the quality criteria not fulfilled, but most important methodological aspects described [inclusion criteria, literature search, quality assessment, details on individual studies (including quality), appropriate statistical analysis]
- poor quality: any others.

The quality of RCTs, identified by any of the methods outlined above, was assessed according to the following criteria [modified from the criteria suggested by the Centre for Reviews and Dissemination (CRD) report on systematic review methodology]:⁷²

- description and method of randomisation
- allocation concealment
- blinding of participants to active agent or placebo
- blinding of outcomes assessors
- numbers of participants randomised, excluded (with reasons) and lost to follow-up
- whether intention-to-treat analysis was performed
- methods for handling missing data
- appropriateness of statistical analysis.

Data extraction

Data were extracted independently by one reviewer using a standardised data extraction table and checked by another. Only a small number of discrepancies occurred, and these were resolved by discussion and by checking the original article.

Data analysis

The systematic reviews included were compared according to the following criteria:

- conclusions reached with respect to the effectiveness of glucosamine and/or chondroitin (in relation to relevant outcome measures)
- any differences in conclusions reached and the reasons for this; for example, inclusion criteria for studies, number and nature of studies included, outcome measures considered, importance placed on study quality or study duration, different forms of glucosamine considered separately (glucosamine sulphate and glucosamine hydrochloride), etc.
- usefulness in addressing our research question about the clinical effectiveness of glucosamine and/or chondroitin in modifying disease progression over at least 12 months.

Data from systematic reviews were tabulated and discussed in a narrative review. Study characteristics of the primary studies included in the reviews were compared against the inclusion criteria of the present review. Characteristics and quality of RCTs fulfilling the inclusion criteria of this review (both those included in previous reviews and studies newly identified) were also tabulated.

For the RCTs, where data permitted (i.e. more than one study available for a given parameter and parameters measured in a comparable way) data from primary studies were summarised in a meta-analysis using the Cochrane Review Manager Software 5.0.4. Continuous data were summarised as weighted mean differences using both fixed- and random-effects models. Where the point estimate was the same, the random-effects model was quoted because the confidence intervals better reflect the uncertainty around the point estimates. No dichotomous results were analysed. Heterogeneity was assessed using the chi-squared test. For outcomes where no meta-analysis was possible, results were summarised narratively.

Results

The results have been presented in two sections. First, we present the findings from the review of systematic reviews. Secondly, we report the results of the review of the primary RCTs that met the criteria for this review.

Review of systematic reviews

Search results

The searches of MEDLINE, EMBASE and the Cochrane Library combined (as shown in Appendix 1) retrieved 677 articles. The duplicates were removed, and the remaining abstracts checked against the inclusion criteria. This resulted in 23 articles, for which the full papers were obtained for further checking. The QUOROM flow diagram of search results is shown in *Figure 2*.

Of the 23 potential relevant systematic reviews, five were included in the analysis. Twelve of the remaining reviews were excluded because they were not systematic reviews (i.e. they did not include a description of their methodology and did not systematically summarise the data). The remaining six were systematic reviews, but one was a review of nutritional supplements in OA specifically excluding glucosamine and chondroitin, one only reported short-term data (up to a maximum of 12 weeks) and the remaining four did not consider structural outcomes (the bibliographies of these four reviews were searched to ensure no individual studies met our inclusion criteria for trials). Details of reasons for study exclusion are shown in Appendix 2.

Of the remaining five reviews, two dealt with glucosamine only,^{62,73} two dealt with chondroitin only^{61,74} and one dealt with both glucosamine and chondroitin.⁷⁵ All five reviews included a meta-analysis. Additionally, a recent NCCCC guideline for the management of OA was identified, which included a systematic assessment of glucosamine and chondroitin.¹ This guideline was used to inform the NICE guideline for the management of OA²⁹ and was the only included review that considered combination therapy with glucosamine and chondroitin. *Table 5* shows details of the five reviews and one guideline included.

Quality of included reviews

Four of the five included reviews were classified as being high quality reviews, with three^{61,62,75} fulfilling all the quality criteria and one⁷³ failing to give details of study selection. One review⁷⁴ was rated as moderate quality, as neither study selection nor data extraction were described and details on statistical analysis were lacking. The guideline¹ described certain methodological aspects rather briefly, but referred to methods manuals which appeared to assure a high quality systematic reviewing process.

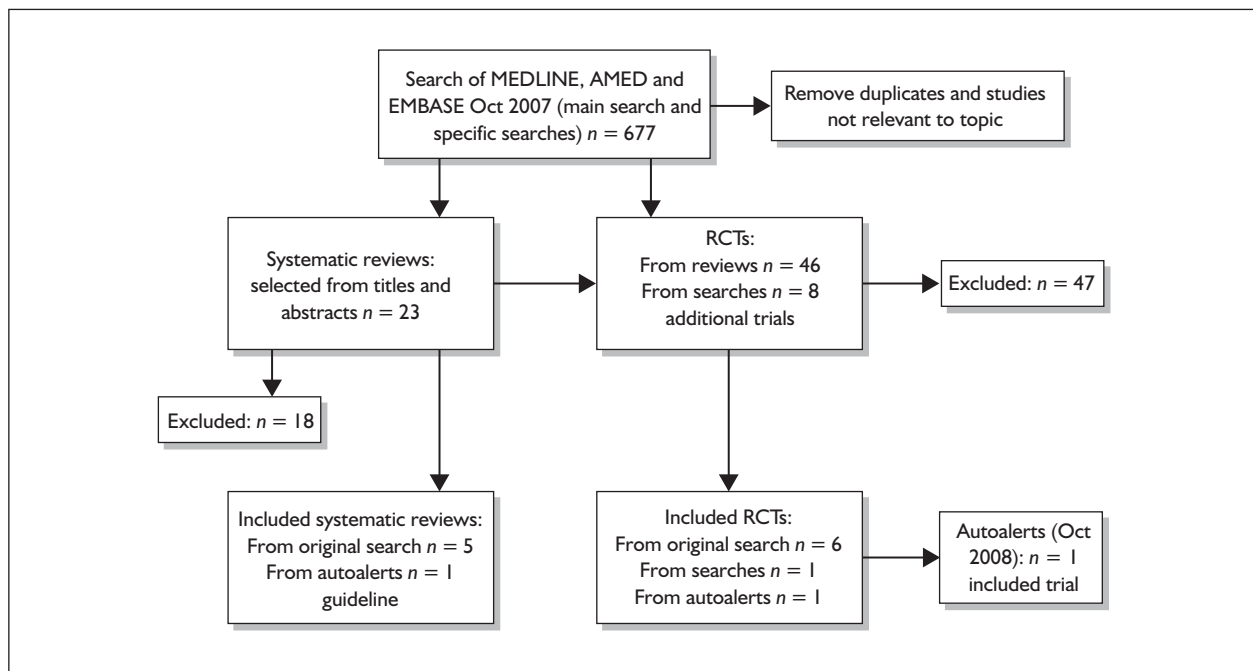


FIGURE 2 QUOROM flow diagram of search results.

Inclusion criteria

Key inclusion criteria and review characteristics are shown in Table 6. The inclusion criteria varied substantially between reviews. One review⁷³ had narrow inclusion criteria, looking at double-blind RCTs lasting at least 12 months and studying the effect of oral glucosamine in primary knee OA. All the studies included in this review, therefore, met with our inclusion criteria of 12 months' duration/follow-up. The other four reviews and one guideline included at least one study of a minimum of 12 months' duration (so were included here), but had wider inclusion criteria and, therefore, also included a number of studies of shorter duration.

Trials included in systematic reviews

The five reviews and one guideline described a total of 45 controlled trials – 21 studying glucosamine, 20 studying chondroitin – and four studying a combination of chondroitin and glucosamine (one of which compared combination therapy with glucosamine or chondroitin monotherapy). Table 7 summarises the characteristics of the 45 primary studies. The NCCCC OA guideline¹ included two systematic reviews^{61,62} and six additional RCTs. For glucosamine, only two RCTs (the long-term studies by Reginster and colleagues⁷⁶ and Pavelká and colleagues⁷⁷) were included in all the relevant reviews. For chondroitin, only six studies were included in all the relevant reviews. The largest number of primary studies was included

in the review by Towheed and colleagues⁶² for glucosamine and Reichenbach and colleagues⁶¹ for chondroitin, and these two reviews also tended to provide the most detail. Therefore, most of the detail presented on the primary studies derives from these two reviews.

The glucosamine trials included between 20 and 1583 participants. With the exception of two trials, the proportion of women included was generally greater than the proportion of men (up to 91% women, with two trials including 48% and 5% women). The mean age range of participants was between 51 and 75 years. Study duration was between 3 weeks and 3 years, with 15 trials having a study duration of no longer than 3 months and two having a duration of at least 1 year. The chondroitin trials included between 17 and 622 participants. As in the glucosamine trials, there were generally more women than men in the trials (33–94%), and mean age was between 50 and 67 years. Trial duration was between 6 weeks and 2 years, with the trials generally having a longer duration than the glucosamine trials (one had a duration of less than 3 months; five had a duration of at least 1 year). One trial, studying a combination of chondroitin and glucosamine, had 1583 participants with a mean age of 58 years and 27% women, and a trial duration of 24 weeks.

Only one of the single therapy and two of the combination therapy trials gave glucosamine

TABLE 5 Characteristics of included systematic reviews and guideline

Study	Inclusion criteria and methodology	Included studies	Quality
<p>Glucosamine</p> <p>Poolsup 2005⁷³</p> <p>Thailand</p> <p>Focus: structural and symptomatic efficacy and safety of glucosamine in knee OA</p>	<p><i>Inclusion criteria</i></p> <p>Study design: double-blind RCTs; study duration at least 1 year</p> <p>Participants: patients with primary knee OA</p> <p>Interventions: oral glucosamine</p> <p>Outcomes: primary outcome – joint space narrowing; additional outcomes – symptom modification, adverse events</p> <p><i>Methodology</i></p> <p>Search strategy: MEDLINE, EMBASE, BIOSIS, Evidence-Based Medicine (EBM) Reviews, Cochrane Library; search from inception of database; scanning of reference lists; search terms indicated; date of last search August 2004</p> <p>Study selection: no details on study selection given</p> <p>Quality assessment: the methodological quality of each study was assessed using the scale developed by Jadad</p> <p>Data extraction: data were extracted independently by two authors; disagreements were resolved by consensus</p> <p>Data analysis: meta-analysis; statistical methodology appropriate</p> <p>Subgroups/sensitivity analyses: none</p>	<p>Number of included trials: 2</p> <p>Number of participants: 414 (range 202–212)</p> <p>Trial quality: Jadad quality scores 4 and 5</p> <p>Study characteristics (comment): both trials fulfil the inclusion criteria of this review; see details of the respective trials below</p>	<p>Inclusion criteria described: yes</p> <p>Details of literature search given: yes</p> <p>Study selection described: no</p> <p>Data extraction described: yes</p> <p>Study quality assessment described: yes</p> <p>Study flow shown: yes</p> <p>Study characteristics of individual studies described: yes</p> <p>Quality of individual studies given: yes</p> <p>Results of individual studies shown: yes</p> <p>Statistical analysis appropriate: yes</p> <p>Overall quality: high</p>
			continued

TABLE 5 Characteristics of included systematic reviews and guideline (continued)

Study	Inclusion criteria and methodology	Included studies	Quality
Towheed 2005 ⁶² Canada (Cochrane review) Focus: effectiveness and toxicity of glucosamine in OA	<p><i>Inclusion criteria</i></p> <p>Study design: RCTs, single or double blind, placebo controlled or active control</p> <p>Participants: adults with primary or secondary OA at any site (not temporomandibular joint)</p> <p>Interventions: glucosamine vs placebo or active control; no combination therapies</p> <p>Outcomes: primary outcomes – pain, range of motion, functional assessments, global assessments; additional outcomes – structural benefits, adverse events</p> <p><i>Methodology</i></p> <p>Search strategy: MEDLINE, EMBASE, Cochrane Controlled Trials Register and Database of Systematic Reviews, AMED, ACP Journal Club, DARE; search from inception of databases; scanning of reference lists; letters to authors and industry for additional trial; detailed search strategy given; date of last search January 2005</p> <p>Study selection: study selection was done independently by two reviewers; if randomisation was unclear, authors were contacted; agreement by consensus</p> <p>Quality assessment: the methodological quality of each study was assessed using the Jadad scale and a scale developed by Gøtzsche for NSAID trials in rheumatoid arthritis (maximum score 8)</p> <p>Data extraction: data were extracted independently by two reviewers; disagreements resolved by consensus</p> <p>Data analysis: meta-analysis; statistical methodology appropriate</p> <p>Subgroups/sensitivity analyses: allocation concealment vs no allocation concealment; Rotta preparation of glucosamine sulphate vs non-Rotta glucosamine preparation</p>	<p>Number of included trials: 20</p> <p>Number of participants: 2596 (range 30–319)</p> <p>Trial quality: Gøtzsche scale mean design and analysis scores 3.7 and 6.3 (of 8, medians similar); mean total scores 10 (of 16). Jadad mean score 4.2. Inadequate allocation concealment in 10 trials</p> <p>Study characteristics (comment): mostly studies with durations of < 1 year (18/20); not all studies investigating only knees; not all studies investigating oral glucosamine; not all studies with placebo control</p>	<p>Inclusion criteria described: yes</p> <p>Details of literature search given: yes</p> <p>Study selection described: yes</p> <p>Data extraction described: yes</p> <p>Study quality assessment described: yes</p> <p>Study flow shown: yes</p> <p>Study characteristics of individual studies described: yes</p> <p>Quality of individual studies given: yes</p> <p>Results of individual studies shown: yes</p> <p>Statistical analysis appropriate: yes</p> <p>Overall quality: high</p>

Study	Inclusion criteria and methodology	Included studies	Quality
<p>Chondroitin Bana 2006⁷⁴ France Focus: symptomatic and structural efficacy and safety of chondroitin sulphate</p>	<p><i>Inclusion criteria</i> Study design: randomised, double-blind, placebo-controlled trials; study duration at least 4 weeks Participants: patients with OA of the knee or hip Interventions: oral chondroitin sulphate Outcomes: symptoms – Lequesne index, WOMAC, investigator's or patient's global assessment; VAS pain, walking time, NSAID or analgesic consumption; structure – mean joint space width, joint surface area, minimum joint space narrowing; adverse events <i>Methodology</i> Search strategy: MEDLINE/PubMed, Cochrane Controlled Trials Register; scanning of reference lists; search terms indicated: limited to studies published in English or French; search limited to studies published in peer-reviewed journals between 1980 and 2005; date of last search 2005 Study selection: no details on study selection given Quality assessment: 14-item quality instrument used by two reviewers; differences resolved by consensus Data extraction: no details on data extraction given Data analysis: meta-analysis; statistical methodology appropriate; however, in two cases the authors included two parts of a single study in their meta-analyses as though they were separate studies – bias? Subgroups/sensitivity analyses: none</p>	<p>Number of included trials: 7 Number of participants: 909 Trial quality: demographic baseline data well matched; quality scores: 6 for one study, 7 for two studies, 9 for one study, 11 for two studies, 13 for one study Study characteristics (comment): three studies lasted a year or longer; authors noted that pain evaluation was biased owing to concomitant consumption of analgesics</p>	<p>Inclusion criteria described: yes Details of literature search given: yes (but limited) Study selection described: no Data extraction described: no Study quality assessment described: yes Study flow shown: yes Study characteristics of individual studies described: yes Quality of individual studies given: yes Results of individual studies shown: yes Statistical analysis appropriate: unclear <i>Overall quality: moderate</i></p>

continued

TABLE 5 Characteristics of included systematic reviews and guideline (continued)

Study	Inclusion criteria and methodology	Included studies	Quality
Reichenbach 2007 ⁶¹ Switzerland/Germany/UK Focus: effects of chondroitin on pain in patients with OA	<p><i>Inclusion criteria</i></p> <p>Study design: randomised or quasi-RCTs</p> <p>Participants: patients with OA of the knee or hip</p> <p>Interventions: chondroitin vs placebo or no treatment; trial groups given low doses excluded (< 400 mg/day administered orally)</p> <p>Outcomes: primary – pain [at end of trial or at a maximum of 3 months after termination of chondroitin therapy (whichever came first)]; when study provided data on more than one pain scale, previously described hierarchy of pain-related outcomes referred to; secondary – changes in mean and minimum joint space width; adverse events (numbers/withdrawals because of/serious)</p> <p><i>Methodology</i></p> <p>Search strategy: Cochrane CENTRAL (1970–2006), MEDLINE (1966–2006), EMBASE (1980–2006), CINAHL (1982–2006); detailed search strategy shown; no language restrictions; extensive supplemental searches; date of last search 30 November 2006</p>	<p>Number of included trials: 22 (20 included in meta-analysis)</p> <p>Number of participants: 4056 (range 17–631)</p> <p>Trial quality: recently performed trials tended to be larger and of higher quality; generation of allocation sequence and allocation concealment unclear for 19 trials; only three trials used intention-to-treat analysis; most trials did not describe approaches for handling missing data; withdrawal rates reported in 13 trials (between 0 and 0.7, most between 0.02 and 0.27); all but three reported to be double blind</p>	<p>Inclusion criteria described: yes</p> <p>Details of literature search given: yes</p> <p>Study selection described: yes</p> <p>Data extraction described: yes</p> <p>Study quality assessment described: yes</p> <p>Study flow shown: yes</p> <p>Study characteristics of individual studies described: yes</p> <p>Quality of individual studies given: yes</p> <p>Results of individual studies shown: yes</p> <p>Statistical analysis appropriate: yes</p> <p>Overall quality: high</p>
	<p>Study selection: two reviewers independently evaluated reports for eligibility; disagreements resolved by discussion</p> <p>Quality assessment: two reviewers independently assessed concealment of treatment allocation, blinding and adequacy of analyses (handling of missing data, intention-to-treat analysis); disagreements resolved by discussion with a third reviewer and consequent consensus; table presented listing study design, allocation concealment, reported to be double blind, adequate blinding of patients, adequate blinding of therapists, described as placebo controlled, withdrawal rate in chondroitin group, withdrawal rate in control group, intention to treat analysis performed, method to handle missing data</p> <p>Data extraction: in duplicate, using standardised form; only first halves of crossover trials used; authors contacted for additional information where necessary; disagreements resolved by discussion with a third reviewer and consequent consensus</p>	<p>Study characteristics (comment): most studies had a short study duration; some studies of non-oral chondroitin and non-knee applications included; noted that unequal consumption of analgesics between comparison groups was an unlikely reason for small effects found</p>	
	<p>Data analysis: meta-analysis; statistical methodology appropriate</p> <p>Subgroups/sensitivity analyses: analyses stratified by – concealment of allocation, use of a placebo control, patient blinding, adequacy of analyses in accordance with the intention-to-treat principle, trial size (cut-off 200 patients), funding, route of administration, length of follow-up (cut-off 26 weeks), difference in use of co-interventions in trial groups; included in univariable meta-regression – chondroitin dosage (in trials with oral administration), treatment duration, length of follow-up</p>		

Study	Inclusion criteria and methodology	Included studies	Quality
<p>Glucosamine/chondroitin NCCCC guideline 2008¹ UK Focus: management of OA</p>	<p><i>Inclusion criteria</i> Study design: systematic reviews, RCTs, (observational studies); trials with sample size < 40 excluded Participants: adults with OA Interventions: glucosamine or chondroitin alone or in compound form vs placebo Outcomes: symptoms, function, QoL, structural changes <i>Methodology</i> Search strategy: MEDLINE (1966 to April 2007), EMBASE (1980 to April 2007), CINAHL (1982 to April 2007), Cochrane Library (April 2007), AMED (1985 to April 2007); search terms not indicated; papers published/accepted by peer-reviewed journals included; conference paper abstracts and non-English language papers excluded Study selection: exclusion lists generated with reasons for exclusions; full papers obtained where relevant Quality assessment: critical appraisal checklists compiled for each paper by one researcher; compliant with NICE technical manual; evidence considered by guideline development group for accuracy and completeness Data extraction: data extracted by one researcher; evidence considered by guideline development group for accuracy and completeness Data analysis: evidence tables and evidence synthesis; evidence statements graded Subgroups/sensitivity analyses: none</p>	<p>Number of included trials: two systematic reviews (Towheed 2005, Reichenbach 2007), six additional RCTs Number of participants: 10,342 (4504 glucosamine trials, 3999 chondroitin trials, 1839 combination glucosamine/chondroitin) Trial quality: all glucosamine trials described as high quality/methodologically sound; all chondroitin and trials of combined glucosamine/chondroitin trials described as methodologically sound Study characteristics (comment): Towheed 2005 and Reichenbach 2007 summarised above; of the additional RCTs included, all have been considered by the present review and were either included or not considered eligible</p>	<p>Criteria described: yes Details of literature search given: partially Study selection described: yes Data extraction described: partially Study quality assessment described: partially Study flow shown: no Study characteristics of individual studies described: partially Quality of individual studies given: yes Results of individual studies shown: yes Statistical analysis appropriate: yes Overall quality: high/moderate</p>

continued

TABLE 5 Characteristics of included systematic reviews and guideline (continued)

Study	Inclusion criteria and methodology	Included studies	Quality
Richy 2003 ⁷⁵ Belgium/France Focus: structural and symptomatic efficacy of glucosamine sulphate and chondroitin sulphate in knee OA	<p><i>Inclusion criteria</i></p> <p>Study design: randomised, double-blind, parallel, placebo-controlled trials performed between January 1980 and March 2002; treatment period at least 4 weeks</p> <p>Participants: patients with OA of the knee or hip</p> <p>Interventions: oral glucosamine or chondroitin</p> <p>Outcomes: at least one of the following outcomes: joint space narrowing, Lequesne index, WOMAC, VAS pain, VAS for mobility assessment, responders to treatment, adverse effects</p> <p><i>Methodology</i></p> <p>Search strategy: MEDLINE, PreMEDLINE, BIOSIS Previews, HealthSTAR, EMBASE, Cochrane Controlled Trials Register, Current Contents, EBM Reviews; search for studies published between January 1980 and March 2002; search terms indicated; no language restrictions; extensive supplemental searches; date of last search March 2002</p> <p>Study selection: potentially relevant publications identified were reviewed by two independent authors for eligibility; in the case of disagreement, a third author was consulted; authors' names and sources were blinded for the selection process</p> <p>Quality assessment: trials fulfilling the inclusion criteria were blindly scored by two reviewers using the Jadad scale; differences were resolved by consensus; authors' names and sources were blinded for quality assessment</p> <p>Data extraction: data for predefined outcomes were extracted blindly by two authors using a standardised form; a third reviewer was consulted in case of disagreement</p> <p>Data analysis: meta-analysis; statistical methodology appropriate; data for glucosamine and chondroitin were analysed together after checking for all outcomes that there were no significant differences between the two compounds</p> <p>Subgroups/sensitivity analyses: none</p>	<p>Number of included trials: 15 (seven glucosamine trials, eight chondroitin trials)</p> <p>Number of participants: 1775 (1020 glucosamine trials, 775 chondroitin trials) (range 24–319)</p> <p>Trial quality: glucosamine trials – three scored 4/5 and four 5/5; chondroitin trials – five scored 3/5, one 4/5, one 5/5, one had insufficient detail; individual demographic baseline data well matched, demographic baseline data for glucosamine and chondroitin trials also well matched</p> <p>Study characteristics (comment): many short-term studies; all studies of knee OA</p>	<p>Criteria described: yes</p> <p>Details of literature search given: yes</p> <p>Study selection described: yes</p> <p>Data extraction described: yes</p> <p>Study quality assessment described: yes</p> <p>Study flow shown: yes</p> <p>Study characteristics of individual studies described: yes</p> <p>Quality of individual studies given: yes</p> <p>Results of individual studies shown: yes</p> <p>Statistical analysis appropriate: yes</p> <p>Overall quality: high</p>
	NSAID, non-steroidal anti-inflammatory drug; QoL, quality of life; RCT, randomised controlled trial; VAS, visual analogue scale.		

TABLE 6 Summary of review characteristics

Poolsup 2005⁷³	Towheed 2005⁶²	Bana 2006⁷⁴	NCCCC guideline 2008¹	Reichenbach 2007⁶¹	Richy 2003⁷⁵
<i>Inclusion</i> RCTs, double blind, duration at least 1 year Primary knee OA Glucosamine vs placebo Joint space narrowing, symptoms, adverse events <i>Quality: high</i> Included trials: 2 (414 participants)	<i>Inclusion</i> RCTs, single or double blind Primary or secondary OA Glucosamine vs placebo or active intervention Pain, range of motion, functional assessment, structural benefits, adverse events <i>Quality: high</i> Included trials: 20 (2596 participants)	<i>Inclusion</i> RCTs, double blind, duration at least 4 weeks OA of the knee or hip Oral chondroitin sulphate vs placebo Symptoms, pain, structure, adverse events <i>Quality: moderate</i> Included trials: 7 (909 participants)	<i>Inclusion</i> Systematic reviews, RCTs OA in adults Glucosamine or chondroitin alone or in compound form vs placebo Symptoms, function, QoL, structural changes <i>Quality: moderate</i> Included trials: 2 systematic reviews, 6 additional RCTs (10,342 participants)	<i>Inclusion</i> Randomised or quasi-randomised controlled trials OA of the knee or hip Chondroitin vs placebo or no treatment Pain, joint space width, adverse events <i>Quality: high</i> Included trials: 22 (4056 participants)	<i>Inclusion</i> RCTs, double blind, duration at least 4 weeks OA of the knee or hip Oral glucosamine or chondroitin vs placebo Joint space width, function, pain, adverse events <i>Quality: high</i> Included trials: 15 [7 glucosamine (1020 participants), 8 chondroitin (775 participants)]
QoL, quality of life; RCTs, randomised controlled trials.					

hydrochloride rather than glucosamine sulphate. One single therapy trial switched from glucosamine sulphate to glucosamine hydrochloride halfway through the trial owing to supply problems for the glucosamine/placebo product initially used. Towheed and colleagues⁶² reported data for nine trials using the Rotta preparation of glucosamine and for eight trials using a non-Rotta preparation. None of the studies included Alateris, the only licensed glucosamine product in the UK.

Findings

The findings of the reviews need to be compared with caution; some reviews were more inclusive than others. Of the glucosamine trials, three did not clearly include only knee OA, four gave glucosamine by injection and five had active rather than placebo control groups (three compared with ibuprofen, two compared with piperazine plus chlorbutanol). These glucosamine trials were included in the review by Towheed and colleagues,⁶² but in none of the others. Of the chondroitin trials, one considered hip rather than knee OA and two gave chondroitin by injection. These chondroitin trials were included in the review by Reichenbach and colleagues,⁶¹ but in none of the others. Reichenbach and colleagues,⁶¹ also included several studies published in abstract form only, although additional information was obtained where possible. Of the combination

therapy trials, three had a duration of less than a year, one studied a topical application of glucosamine and chondroitin, and two examined no structural outcomes. These combination therapy studies were included in the NCCCC OA guideline 2008.¹

Appendix 3 summarises the results of the meta-analyses of the included reviews and Appendix 4 shows the results of any relevant subgroup or sensitivity analyses. Fundamental to our research question, none of the reviews presented data separately for trials of longer duration for all outcomes. For structural changes, most of the trial data have been limited to longer trials, so conclusions from three of the reviews were based solely on trials of more than 1-year follow-up. The other two reviews, and the guideline, based their conclusions about structural changes on a mixture of shorter- and long-term studies

As the NCCCC OA guideline¹ focused mainly on two systematic reviews already included here and the only additional RCT eligible for the present review is already described below, the results of that guideline are not shown in further detail. *Table 8* summarises the conclusions and recommendations of the reviews. Trials and reviews are hereafter referred to by the name of the first author.

TABLE 7 Distribution of primary studies in the included reviews

	Glucosamine only		Chondroitin only		Both	
	Poolsup 2005 ⁶⁵	Towheed 2005 ⁷³	Bana 2006 ⁷⁴	Reichenbach 2007 ⁶¹	NCCCC 2008 ¹	Richy 2003 ⁷⁵
Glucosamine						
Cibere 2004 ⁷⁸		✓			✓	
Crolle 1980 ⁷⁹					✓	
D'Ambrosio 1981 ⁸⁰		✓			✓	
Drovanti 1980 ⁸¹					✓	
Herrero-Beaumont 2007 ⁸²					✓	
Haupt 1999 ⁸³		✓			✓	
Hughes 2002 ⁸⁴					✓	✓
McAlindon 2004 ⁸⁵		✓			✓	
Müller-Fassbender 1994 ⁸⁶		✓			✓	
Noack 1994 ⁸⁷		✓			✓	✓
Pavelká 2002 ⁷⁷		✓			✓	✓
Pujalte 1980 ⁸⁸					✓	✓
Qiu 1998 ⁸⁹		✓			✓	
Reginster 2001 ⁷⁶		✓			✓	✓
Reichelt 1994 ⁹⁰					✓	
Rindone 2000 ⁹¹		✓			✓	✓
Rovati 1997 ⁹²					✓	✓
Usha 2004 ⁹³		✓			✓	
Vajjaradul 1981 ⁹⁴					✓	
Vaz 1982 ⁹⁵		✓			✓	
Zenk 2002 ⁹⁶					✓	
Chondroitin						
Alekseeva 1999 ⁹⁷				✓	✓	
Bourgeois 1998 ⁹⁸			✓	✓	✓	✓
Bucsi 1998 ⁹⁹			✓	✓	✓	✓
Conrozier 1992 ¹⁰⁰				✓	✓	
Fleisch 1997 ¹⁰¹				✓	✓	
Kahan 2007 ¹⁰²				✓	✓	
Kerzberg 1987 ¹⁰³				✓	✓	
L'Hirondel 1992 ¹⁰⁴				✓	✓	✓
Mazieres 1992 ¹⁰⁵			✓	✓	✓	✓
Mazieres 2001 ¹⁰⁶			✓	✓	✓	✓
Mazieres 2007 ¹⁰⁷				✓	✓	
Michel 2005 ¹⁰⁸			✓	✓	✓	
Morreale 1996 ¹⁰⁹				✓	✓	
Nasonova 2001 ¹¹⁰				✓	✓	
Pavelká 1999 ¹¹¹				✓	✓	✓
Rovetta 1991 ¹¹²				✓	✓	

TABLE 7 Distribution of primary studies in the included reviews (continued)

	Glucosamine only		Chondroitin only		Both	
	Poolsup 2005 ⁶⁵	Towheed 2005 ⁷³	Bana 2006 ⁷⁴	Reichenbach 2007 ⁶¹	NCCCC 2008 ¹	Richy 2003 ⁷⁵
Soroka 2002 ¹¹³				✓	✓	
Uebelhart 1998 ¹¹⁴			✓	✓	✓	✓
Uebelhart 1999 ¹¹⁵				✓	✓	
Uebelhart 2004 ¹¹⁶			✓	✓	✓	✓
Glucosamine/chondroitin						
Clegg 2006 ¹¹⁷				✓	✓	
Cohen 2003 ¹¹⁸					✓	
Das 2000 ¹¹⁹					✓	
Rai 2004 ¹²⁰					✓	

Glucosamine

Structure For glucosamine, only two trials were included in the analysis of structural outcomes in all the three relevant systematic reviews (including the Richy review where only glucosamine trials were included in the analysis of structural outcomes), namely the trials by Reginster⁷⁶ and Pavelká.⁷⁷ Both the Poolsup⁷³ and Towheed⁶² reviews concluded that glucosamine may delay the structural progression of OA of the knee.

Symptoms/pain While Poolsup⁷³ concluded that their results showed evidence in support of an improvement of symptoms with glucosamine sulphate, Towheed⁶² was more cautious. They stated that overall, glucosamine was shown to have a moderate clinically significant effect on pain compared with placebo. With respect to function, results were mixed, with significant results for the Lequesne index, but not for the WOMAC total score or any of the WOMAC subscores; in their subgroup analyses, results were only significant for pain and the WOMAC total score for studies using the Rotta preparation of glucosamine, while they were non-significant for trials using a non-Rotta preparation. Poolsup⁷³ only considered long-term studies (whereas Towheed⁶² included mainly short-term studies) and commented that an effect on physical function may only be achieved with long-term use of glucosamine.

Adverse events Both reviews concluded that glucosamine was safe. Towheed⁶² did, however, mention the concern and uncertainty with respect to a possible effect of glucosamine on glucose metabolism; while not including this particular question in their review, they did quote two studies specifically addressing this question that found

no evidence of an adverse metabolic effect of glucosamine.

Chondroitin

Structure Both the review by Bana⁷⁴ and the review by Reichenbach⁶¹ came to similar conclusions with respect to the structural benefits of chondroitin sulphate. Both suggested a small effect on joint space width in favour of chondroitin, with uncertain clinical significance (and possibly in the absence of a functional benefit). They considered the same two trials of more than one year follow-up (with the addition of one further shorter study included in the Reichenbach review⁶¹).

Symptoms/pain Both Bana⁷⁴ and Reichenbach⁶¹ were cautious in their interpretation of the data with respect to benefits of chondroitin sulphate on joint pain and function. Bana⁷⁴ concluded that there was a true, but modest, effect of pain relief and improvement of function but also concluded that the results were probably biased owing to the poor quality of the data. They pointed out that pain evaluation was complicated in most studies as concomitant analgesic or NSAID use was allowed, but actual consumption was often not reported in detail. They also observed a latency period of about a month before an advantage of chondroitin with respect to pain relief and function was seen, as well as an effect lasting beyond the cessation of treatment, which they thought might justify cycles of treatment to be used.

Reichenbach⁶¹ stressed the high degree of heterogeneity between studies and the poor quality of many studies and concluded that large-scale methodologically sound trials indicated that the symptomatic effect of chondroitin sulphate was

TABLE 8 Conclusions and recommendations of reviews

Study	Authors' conclusions	Recommendations for research	Additional comments
Glucosamine			
Poolsup 2005 ⁷³	<p><i>Pain/function:</i> The results showed evidence in support of an improvement of symptoms by glucosamine sulphate</p> <p><i>Structure (based on two studies of > 1-year follow-up):</i> The results showed evidence in support of a delay of structural progression by glucosamine sulphate</p> <p><i>Adverse effects:</i> The evidence suggests that glucosamine sulphate is safe in long-term use</p>	<p>High quality, placebo-controlled long-term trials of various forms (different salts, different forms of glucosamine sulphate) of glucosamine are needed</p>	<p>An effect on physical function may only be achieved during long-term use</p>
Towheed 2005 ⁶²	<p><i>Pain/function:</i> Overall, glucosamine showed a moderate clinically significant effect on pain compared with placebo. Pooled results from studies using a non-Rotta preparation of glucosamine or adequate allocation concealment failed to show benefit in pain and WOMAC function, while those studies evaluating the Rotta preparation showed that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic osteoarthritis. WOMAC outcomes of pain, stiffness and function did not show a superiority of glucosamine over placebo for both Rotta and non-Rotta preparations of glucosamine</p> <p><i>Structure (based on three studies of variable follow-up):</i> Glucosamine may modify the natural radiological progression of osteoarthritis of the knee (delaying progression)</p> <p><i>Adverse effects:</i> Glucosamine was as safe as placebo</p>	<p><i>Questions remaining to be answered</i></p> <p>Are different glucosamine preparations sold by different manufacturers equally effective and safe in the therapy of OA?</p> <p>Is glucosamine sulphate equally effective as glucosamine hydrochloride?</p> <p>Is there any further benefit obtained by using mixed glucosamine preparations that contain additional therapeutic products, such as chondroitin sulphate?</p> <p>Is glucosamine helpful for all stages of OA severity?</p> <p>What is the optimal dose for maximising efficacy and minimising toxicity?</p> <p>What are the patient specific predictors of favourable effects on radiological progression of OA?</p>	<p>There is uncertainty about the effect of glucosamine on glucose metabolism with long-term use – no evidence of an adverse effect was found by two studies</p>
Chondroitin			
Bana 2006 ⁷⁴	<p><i>Pain/function:</i> The results analysed suggested a true, but modest effect of chondroitin sulphate on relief of pain and improvement of joint function in patients treated. However, the authors concluded that the evaluation could be biased, as only few methodologically sound papers were available</p> <p><i>Structure (based on three studies > 1 year):</i> Structure (mean and minimum joint space width) appears to be preserved with chondroitin sulphate (versus deterioration in the placebo groups), but in the main study showing a structural advantage, no effect on the WOMAC score was seen</p> <p><i>Adverse effects:</i> The tolerance of chondroitin sulphate can be considered as excellent</p>	<p>Further large studies lasting at least 2 years are needed to confirm any effects of chondroitin sulphate on preservation of structure/ joint space width</p> <p>Studies needed to ascertain for which OA patients these drugs are useful (e.g. patients with mild to moderate disease)</p>	<p>Pain evaluation is biased as in most studies concomitant analgesic/ NSAID use is allowed – but often not reported in detail</p> <p>A latency period of about 1 month was observed before an advantage of chondroitin for pain relief/ function could be seen</p> <p>The activity of chondroitin appears to last for up to 3 months after the drug is stopped, so cycles of treatment/no treatment might be justified</p>

TABLE 8 Conclusions and recommendations of reviews (continued)

Study	Authors' conclusions	Recommendations for research	Additional comments
Reichenbach 2007 ⁶¹	<p><i>Pain/function:</i> There was a high degree of heterogeneity between trials, making interpretation difficult; most studies were poor quality; large-scale, methodologically sound trials indicate that the symptomatic benefit of chondroitin is minimal or non-existent</p> <p><i>Structure (based on five studies of varying duration):</i> A small effect on joint space width in favour of chondroitin was seen, with uncertain clinical significance</p> <p><i>Adverse effects:</i> No evidence was found that chondroitin is unsafe</p> <p><i>Practice recommendation:</i> The use of chondroitin in routine clinical practice should be discouraged. In patients with advanced OA an effect is unlikely; in patients with low-grade OA use of chondroitin should be restricted to RCTs</p>	<p>Future trials should adhere to methodological standards reducing possible biases; reporting should adhere to standards such as the CONSORT criteria</p> <p>A rigorously designed, adequately powered, randomised placebo-controlled trial restricted to patients with low-grade OA would be needed to assess if chondroitin is more effective in patients with mild disease than in patients with more severe disease</p>	<p>A significantly <i>larger</i> effect of chondroitin was seen in trials in which use of rescue analgesics was reported to be higher in the control groups</p> <p>Concomitant use of medication (analgesics, NSAIDs) was poorly reported – but small/lack of effect seen was unlikely to be related to concomitant analgesic/NSAID use</p> <p>Recently performed methodologically sound trials with effect sizes near zero tended to have lower proportions of patients with low-grade OA – but the effect of chondroitin may depend on OA stage</p>
Glucosamine/chondroitin			
NCCCC guideline 2008 ¹	<p><i>General/pain/function/adverse events:</i> The evidence from the trials is often difficult to compare owing to differences in the products used (and their bioavailability), between-study populations, patient BMI, and the use of analgesia at the time of pain and function assessment in the trials. Overall, trials using glucosamine sulphate as a single dose of 1500 mg rather than hydrochloride 500 mg three times a day showed a small benefit compared with placebo for treatment of knee OA. However, at the time the guideline was prepared, the hydrochloride preparation has been granted a European Medicines Evaluatory Agency licence, while the sulphate has not. The evidence for efficacy of chondroitin was less convincing</p> <p>Evidence to support the efficacy of glucosamine hydrochloride as a symptom modifier is poor. For the non-licensed product (glucosamine sulphate), the evidence is not strong enough to warrant recommending that it should be prescribed on the NHS. Notwithstanding some evidence of benefit and very little evidence of harm in clinical practice, and despite the extra scrutiny these agents have received, the economic cost–consequence table shows that only glucosamine sulphate is potentially cost-effective out of the interventions considered in this section.</p>	<p>Study of short- and long-term effects in the very elderly</p> <p>Benefits of individual and combination OA therapies in people with multiple joint region pain</p> <p>Identifying subsets of people with OA in whom existing treatments are more beneficial and cost-effective</p>	

continued

TABLE 8 Conclusions and recommendations of reviews (continued)

Study	Authors' conclusions	Recommendations for research	Additional comments
Richy 2003 ⁷⁵	<p>A wide range of ICERs were reported and the poorest estimates of efficacy would take it beyond the threshold of affordability in the NHS. Because only one glucosamine hydrochloride product is licensed, it would not be cost-effective to prescribe glucosamine on the NHS</p> <p>Many people with OA take over-the-counter nutraceutical products and may benefit from clear, evidence-based information. In particular, the guideline development group felt that it would be beneficial to advise people who wanted to trial over-the-counter glucosamine that the only potential benefits identified in early research are related purely to a reduction of pain (to some people, and to only mild or modest degree) with glucosamine sulphate 1500 mg daily. They could also benefit from advice on how to perform their own trial of therapy, that is, to evaluate their pain before starting glucosamine and ensure they review the benefits of glucosamine after 3 months</p> <p><i>Structure:</i> In assessing the outcomes given in the evidence base, the guideline development group regarded measurement of joint space narrowing as of questionable value in assessing any potential beneficial structural modification, and convincing evidence of improvement in patient-centred outcomes consequent on any structural modification is still lacking. There is therefore no positive recommendation regarding structure modification</p> <p><i>Overall recommendation:</i> The use of glucosamine or chondroitin products is not recommended for the treatment of OA</p> <p><i>Pain/function:</i> Comparable symptomatic efficacies (Lequesne index, VAS pain and mobility) of chondroitin and glucosamine were shown</p>	<p>Long-term studies are needed to confirm and evaluate the structural efficacy of chondroitin</p> <p>For glucosamine, further studies on the relationship between structural and symptomatic changes, controlling for baseline characteristics including OA stage, are needed, as well as studies on the possible use of glucosamine in prevention</p>	<p>It is important to note that rescue medications were allowed in all trials; however, cumulative doses were low and it might be unlikely that rescue medication affected the pain-relieving effect of glucosamine and chondroitin</p>
<p>BMI, body mass index; CONSORT, Consolidated Standards of Reporting Trials; ICERs, incremental cost-effectiveness ratios; NSAIDs, non-steroidal anti-inflammatory drugs; RCTs, randomised controlled trials; VAS, visual analogue scale.</p>			

minimal or non-existent. They suggested that if there was an effect, chondroitin sulphate was more likely to benefit patients with low-grade OA than patients with advanced OA. They also mentioned the problem of concomitant use of rescue analgesia, but observed that in trials where use of rescue analgesia was reported to be greater in the placebo group, the effect of chondroitin sulphate was actually reported to be larger than in trials reporting equal use in both comparison groups.

Adverse events Both reviews concluded that chondroitin sulphate was safe.

Glucosamine and/or chondroitin

Analysing trials of glucosamine or chondroitin versus placebo together in one meta-analysis, Richy⁷⁵ found glucosamine/chondroitin to be superior to placebo for all the outcomes investigated. The authors concluded that glucosamine sulphate or chondroitin sulphate had a comparable benefit with respect to symptomatic outcomes (Lequesne index, VAS pain and mobility). Authors reported that adequate structural data were only available for glucosamine, and a statistically significant benefit in the low to medium range was reported. Exclusion of structural data from certain chondroitin studies was a result of inadequately detailed reporting. The authors mentioned the concomitant use of rescue medication, but concluded that cumulative doses were low and that rescue medication was unlikely to have affected the pain-relieving effect of glucosamine and chondroitin.

The NCCCC OA guideline¹ did not recommend the use of glucosamine or chondroitin products for use in OA. They concluded that the evidence from the trials was often difficult to compare owing to differences in the products used (and their bioavailability), between-study populations, patient BMI, and the use of analgesia at the time of pain and function assessment in the trials. They found that, overall, trials using glucosamine sulphate as a single dose of 1500 mg rather than hydrochloride at 500 mg three times a day showed a small benefit compared with placebo for treatment of knee OA. However, at the time the guideline was prepared, the hydrochloride preparation had been granted a European Medicines Evaluatory Agency licence, while the sulphate had not. The evidence for efficacy of chondroitin was less convincing.

Their results suggested that the evidence to support the efficacy of glucosamine hydrochloride as a symptom modifier was poor, and for the

non-licensed product (glucosamine sulphate), the evidence was not strong enough to warrant recommending that it should be prescribed on the NHS. Notwithstanding some evidence of benefit and very little evidence of harm in clinical practice, and despite the extra scrutiny these agents had received, their economic cost–consequence table showed that only glucosamine sulphate was potentially cost-effective out of the interventions considered in this section; however, a wide range of incremental cost-effectiveness ratios (ICERs) was reported and the poorest estimates of efficacy would take it beyond the threshold of affordability in the NHS. Because only a glucosamine hydrochloride product was licensed, it would not be cost-effective to prescribe glucosamine on the NHS.

The guideline, however, also stated that many people with OA take over-the-counter nutraceutical products and may benefit from clear, evidence-based information. In particular, the guideline development group felt that it would be beneficial to advise people who wanted to trial over-the-counter glucosamine that the only potential benefits identified in early research were related purely to a reduction of pain (to some people, and to only a mild or modest degree) with glucosamine sulphate 1500 mg daily. They could also benefit from advice on how to perform their own trial of therapy, that is, to evaluate their pain before starting glucosamine and ensure they review the benefits of glucosamine after 3 months.

With respect to structural outcomes, the guideline development group regarded measurement of joint space narrowing as of questionable value in assessing any potential beneficial structural modification, and convincing evidence of improvement in patient-centred outcomes consequent on any structural modification was still lacking. There was therefore no positive recommendation regarding structure modification.

Research recommendations and conclusions from the systematic reviews

Table 8 summarises the researchers' conclusions and recommendations from the reviews and guideline. The conclusions about clinical effectiveness of glucosamine and chondroitin were not consistent. Authors noted that, at best, a modest effect on pain and function was observed. The effect on joint space was more consistent, but again the effect size was considered to be small and the long-term significance was hampered by the lack of long-term follow-up studies. The variability in quality of some of the trials, in particular for chondroitin,

was noted, as was the variability in the preparations used.

For the purposes of our research question about the effectiveness in modifying long-term disease progression, the reviews we identified, with the exception of Poolsup,⁷³ included only a very small proportion of trials of adequate follow-up. While conclusions regarding structural changes were, in three of the six reviews and guidelines, based on studies of at least 1 year, none presented their data for long-term QoL outcomes separately. In addition, the reporting of data extracted from primary studies varied in the reviews with some inconsistencies. We therefore went on to review RCTs of at least 12 months' duration or follow-up and the results are reported below.

Review of randomised controlled trials

Search results

The range of trials included in the reviews presented above varied widely and it proved difficult to apply the findings to assessing the effectiveness of glucosamine and chondroitin on long-term outcomes such as disease progression. In addition, the reporting of the reviews on primary studies was not always consistent as not all reviews described all the details about the primary studies. We have, therefore, reviewed separately all the primary studies fulfilling our inclusion criteria (both the ones included in the reviews and new ones identified in our searches and not included in the reviews).

Within the reviews included above, there were only two glucosamine RCTs fulfilling the inclusion criteria of our review,^{76,77} three chondroitin trials^{108,114,116} (an earlier publication, Conrozier 1998,¹²¹ is included in the Reichenbach review⁶¹), and one combination therapy trial.¹²⁰

Table 9 compares the characteristics of the primary studies included in the systematic reviews against the inclusion criteria of our review. The most frequent reason for not fulfilling the inclusion criteria of the present review was short study duration (18 glucosamine, 15 chondroitin and one combined glucosamine/chondroitin trial).

In addition, *Table 9* includes the details of studies identified in our additional searches. Through examination of the excluded reviews and through supplemental searches, we identified four further RCTs studying glucosamine, and four studying a combination of glucosamine and chondroitin.

However, only one trial fulfilled our inclusion criteria,¹²² reporting only on symptoms, but not on structure. A fifth trial was identified through a PubMed auto-alert in June 2008. Kawasaki¹²³ reported both on symptoms and on structure. For details of reasons for trial exclusion, see *Table 9*.

One study excluded from our review is worthy of noting here because of its high profile: the GAIT (Glucosamine/chondroitin Arthritis Intervention Trial) study, funded by the National Institute of Health (NIH) and conducted in multiple centres across the USA.¹¹⁷ The original study was an RCT of 24 weeks' duration and was thus excluded from our review.¹¹⁷ Recently (October 2008) a further report was published with 24 months of follow-up.¹²⁴ This report is of a subset of participants in the original trial who met certain criteria and who accepted an invitation to participate in the longer follow-up. Inclusion in the follow-up study required that patients had appropriate baseline imaging and continued on treatment and participating in follow-up at least until repeat imaging was done at 12 months. The authors describe the subsequent study as a prospective observational study.¹²⁴ Substantial numbers of patients who were eligible for this extension study were not included in the analysis; the most common reason was withdrawal prior to completing 12 months of follow-up. For example, in the glucosamine arm of the study, 134 patients were eligible, but only 77 were analysed, with 33 withdrawing from the study. The withdrawals were not described. The resulting study is at high risk of biases around participation, where patients who dropped out were likely to differ, in a non-random way, from those who continued. The baseline characteristics of patients participating in the extension study differed between groups with regard to sex, symptoms, radiological grade and BMI.

The eight studies fulfilling our inclusion criteria are highlighted in grey in *Table 9*.

The eight trials included did not allow a detailed comparison of different glucosamine preparations (sulphate versus hydrochloride or Rotta versus non-Rotta preparations). Similarly, none of the trials included a comparison between glucosamine and chondroitin, or a comparison between glucosamine and chondroitin combination therapy with either glucosamine or chondroitin monotherapy. Likewise, none of the trials compared different doses of the treatment.

Table 10 summarises the characteristics of the included trials. The results for glucosamine and

TABLE 9 Randomised controlled trials (RCTs) included in reviews and identified in additional searches against inclusion criteria for this review (highlighted trials met all of the inclusion criteria for this review)

RCT	Knee OA	Duration ≥ 1 year	Oral medication	Placebo control	Structural outcomes included	Full text publication
Glucosamine						
From systematic reviews						
Cibere 2004 ⁷⁸	✓	No	✓	✓	No	✓
Clegg 2006 ¹¹⁷	✓	No	✓	✓	No	✓
Crolle 1980 ⁷⁹	?	No	No	No	No	✓
D'Ambrosio 1981 ⁸⁰	Various sites	No	No	No	No	✓
Drovanti 1980 ⁸¹	Various sites	No	✓	✓	No	✓
Herrero-Beaumont 2007 ⁸²	✓	No	✓	✓	No	✓
Houpt 1999 ⁸³	✓	No	✓	✓	No	✓
Hughes 2002 ⁸⁴	✓	No	✓	✓	No	✓
McAlindon 2004 ⁸⁵	✓	No	✓	✓	No	✓
Müller-Fassbender 1994 ⁸⁶	✓	No	✓	No	No	
Noack 1994 ⁸⁷	✓	No	✓	✓	No	✓
Pavelká 2002 ⁷⁷	✓	✓	✓	✓	✓	✓
Pujalte 1980 ⁸⁸	✓	No	✓	✓	✓	✓
Qiu 1998 ⁸⁹	✓	No	✓	No	No	✓
Reginster 2001 ⁷⁶	✓	✓	✓	✓	✓	✓
Reichelt 1994 ⁹⁰	✓	No	No		No	✓
Rindone 2000 ⁹¹	✓	No	✓	✓	No	✓
Rovati 1997 ⁹²	✓	No	✓	✓	No	?
Usha 2004 ⁹³	✓	No	✓	✓	No	✓
Vajaradul 1981 ⁹⁴	✓	No	No	✓	No	✓
Vaz 1982 ⁹⁵	✓	No	✓	No	No	✓
Zenk 2002 ⁹⁶	✓	No	✓	✓	No	✓
Additional searches						
Braham 2003 ¹²⁵	?	No	✓	✓	No	✓
Frestedt 2008 ¹²⁶	✓	No	✓	✓	No	✓
Mehta 2007 ¹²⁷	✓	No	✓	No	No	✓
Zhang 2007 ¹²⁸	✓	No	✓	No	No	✓
Chondroitin						
From systematic reviews						
Alekseeva 1999 ⁹⁷		No	✓	✓	No	✓
Bourgeois 1998 ⁹⁸	✓	No	✓	✓	No	✓
Bucsi 1998 ⁹⁹	✓	No	✓	✓	No	✓
Conrozier 1992 ¹⁰⁰	No	No	✓	✓	No	✓
Fleisch 1997 ¹⁰¹	✓	✓	✓	✓	No	No

continued

TABLE 9 Randomised controlled trials (RCTs) included in reviews and identified in additional searches against inclusion criteria for this review (highlighted trials met all of the inclusion criteria for this review) (continued)

RCT	Knee OA	Duration ≥ 1 year	Oral medication	Placebo control	Structural outcomes included	Full text publication
Kahan 2007 ¹⁰²	✓	✓	✓	✓	✓	No
Kerzberg 1987 ¹⁰³	✓	No	No	✓	No	✓
L'Hirondel 1992 ¹⁰⁴	✓	No	✓	✓	No	✓
Mazieres 1992 ¹⁰⁵	✓	No	✓	✓	No	✓
Mazieres 2001 ¹⁰⁶	✓	No	✓	✓	No	✓
Mazieres 2007 ¹⁰⁷	✓	No	✓	✓	No	✓
Michel 2005 ¹⁰⁸	✓	✓	✓	✓	✓	✓
Morreale 1996 ¹⁰⁹	✓	No	✓	✓	No	✓
Nasonova 2001 ¹¹⁰	✓	No	✓	✓	No	✓
Pavelká 1999 ¹¹¹	✓	No	✓	✓	No	✓
Rovetta 1991 ¹¹²	✓	No	No		No	✓
Soroka 2002 ¹¹³	✓	No	✓	✓	No	No
Uebelhart 1998 ¹¹⁴ /Conrozier 1998 ¹²¹	✓	✓	✓	✓	✓	✓
Uebelhart 1999 ¹¹⁵	✓	No	✓	✓	No	No
Uebelhart 2004 ¹¹⁶	✓	✓	✓	✓	✓	✓
Glucosamine/chondroitin						
From systematic reviews						
Clegg 2006 ¹¹⁷	✓	No	✓	✓	No	✓
Cohen 2003 ¹¹⁸	✓	No	No		No	✓
Das 2000 ¹¹⁹	✓	No	✓	✓	✓	✓
Rai 2004 ¹²⁰	✓	✓	✓	✓	✓	✓
Additional searches						
Messier 2007 ¹²²	✓	✓	✓	✓	No	✓
Kawasaki 2008 ¹²³	✓	✓	✓	✓	✓	✓
Debi 2000 ¹²⁹	✓	No	No	✓	No	✓
Leffler 1999 ¹³⁰	✓	?	?, not only GI/Ch	✓	No	✓
Nguyen 2001 ¹³¹	No	No	✓	✓	No	✓

Ch, chondroitin; GI, glucose.

chondroitin are presented separately. Appendix 5 provides all of the data in a single summary table for direct comparison between treatments.

Findings

Glucosamine

Trial characteristics

Three trials compared glucosamine with placebo. The trials by Pavelká⁷⁷ and Reginster⁷⁶ were both randomised, double-blind, placebo-controlled trials with a duration of 3 years. Follow-up data for knee arthroplasty for both trials taken together were available for a mean follow-up of 8 years (5 years

after cessation of treatment⁵²). Both were funded by the Rotta Research Group. The third trial, by Kawasaki¹²³ was a Japanese open-label RCT with a duration of 18 months.

A total of 556 people participated in these trials. The mean age of participants was between 61 and 70 years and more women than men were included (between 75% and 100% women). Most had OA of Kellgren–Lawrence grade 2 at baseline (between 53% and 54% for Pavelká and between 70% and 71% for Reginster); the rest had OA of Kellgren–Lawrence grade 3 (no details given in the trial by

TABLE 10 Characteristics of randomised controlled trials fulfilling the inclusion criteria of this review

Study	Design	Participants	Interventions	Outcome measures	Quality
Glucosamine Kawasaki 2008 ²³ Japan	Focus: effects of glucosamine, risedronate or no treatment in patients with mild to moderate knee OA concurrently performing therapeutic exercise Single centre Duration: 18 months Follow-up: no post-intervention follow-up Setting: outpatient Funding: not reported	Total number: 142 Glucosamine: n = 49; 31 completed trial Risedronate: n = 51; 33 completed trial (not considered here) Control: n = 42; 30 completed trial Inclusion criteria: postmenopausal women with untreated OA of medial femorotibial compartment of knee and no other inflammatory diseases; selected according to criteria of ACR; joint space width \geq 1 mm or and < 6 mm (equivalent to K-L grade II or III) Exclusion criteria: standard exclusion criteria (references given) Age: glucosamine: 68.5 years, SD 7.3; control: 69.5 years, SD 7.1 Gender: all female BMI: glucosamine: 23.9 kg/m ² , SD 2.5; control: 24.0 kg/m ² , SD 3.0 OA stage: not reported OA duration: not reported Comorbidities: not reported Subgroups: effects of age, BMI, level of joint progression, urine NTX, concomitant use of glucosamine or risedronate with home exercise at baseline (but not for intervention groups separately)	Glucosamine: 1500 mg/day glucosamine hydrochloride Risedronate: 2.5 mg/day risedronate (not considered here) Control: no supplement All groups: instructed by physical therapists to perform home exercise; instruction also given in a brochure; exercises as follows: 1. isometric muscle exercises of the lower limbs, 2. range of motion exercise after the knee was warmed (bath or shower) Co-interventions/rescue analgesia: sodium loxoprofen prescribed in advance for rescue and any use of the medicine recorded Rescue analgesia use: no significant difference between groups Adherence assessment: not reported	Primary: unclear Pain: WOMAC pain subscale, VAS pain scale WOMAC: reported Function: Japan Orthopaedic Association (JOA) score (pain during walking, pain when using stairs, range of motion, swelling, 100 points = full score); WOMAC joint space loss: tibiofemoral joint space width (determined at the centre point of the medial femoral condyle) Adverse events: no Other: NSAID consumption, urinary NTX (uNTX, bone absorption marker) Assessment: regular assessment every 3 months	Method of randomisation: method not described Allocation concealed? Unclear Participants blinded? No Outcome assessors blinded? No; assessment of joint space width blinded Proportion of participants excluded/lost to follow-up: glucosamine: 35% withdrawals; C: 29% withdrawals; no significant difference in rates or reasons Handling of missing data: last observation carried forward Intention-to-treat analysis performed? Yes Statistical analysis appropriate? Yes Groups comparable at baseline? Yes

continued

TABLE 10 Characteristics of randomised controlled trials fulfilling the inclusion criteria of this review (continued)

Study	Design	Participants	Interventions	Outcome measures	Quality
Pavelká 2002 ⁷⁷ Czech Republic	<p>Focus: long-term effects of glucosamine sulphate on progression of joint structure and symptom changes in knee OA</p> <p>Single centre</p> <p>Duration: 3 years</p> <p>Follow-up: no post-intervention follow-up</p> <p>Setting: outpatient</p> <p>Funding: Rotta Research Group (Italy)</p>	<p>Total number: 202</p> <p>Intervention: $n = 101$; 66 completed trial</p> <p>Control: $n = 101$; 55 completed trial</p> <p>Inclusion criteria: 45–70 years, primary knee OA based on clinical and radiological criteria of ACR; Lequesne index at least 4 points, but not > 12</p> <p>Exclusion criteria: history of other clinically significant articular or rheumatic diseases, inflammatory rheumatic disease, secondary OA, history of trauma or lesions of knee joint, severe articular inflammation, evidence of rapidly progressing OA (obtained before the trial); BMI $> 27 \text{ kg/m}^2$, clinically significant alterations in haematological variables and renal, hepatic and metabolic functions; systemic or intra-articular corticosteroid therapy in previous 3 months</p> <p>Age: intervention: 61.2 years, SD 7.3; control: 63.5 years, SD 6.9</p> <p>Gender: intervention: 79% female; control: 76% female</p> <p>BMI: intervention: 25.7 kg/m^2, SD 2.1; control: 25.7 kg/m^2, SD 1.8</p> <p>OA stage: intervention: 54% K–L grade 2, 46% grade 3; control: 53% K–L grade 2, 47% grade 3</p> <p>OA duration: intervention: 10.1 years, SD 8.1; control: 11.0 years, SD 6.8</p> <p>Comorbidities: not reported</p> <p>Subgroups: none</p>	<p>Intervention: 1500 mg/day glucosamine sulphate (powder for oral solution) (Rotta)</p> <p>Control: placebo packets identical in external appearance</p> <p>Co-interventions/rescue analgesia: paracetamol 500 mg tablets, use recorded in patient diaries; no other pharmacologic treatments for OA allowed; only hydrotherapy, exercise or ultrasound allowed as physical therapies (no significant difference between groups)</p> <p>Rescue analgesia use: no significant difference between groups</p> <p>Adherence assessment: at least 86% of patients reported more than 90% drug intake</p>	<p>Primary: changes of minimum joint space width</p> <p>Pain: WOMAC joint pain subscale</p> <p>WOMAC: reported</p> <p>Function: WOMAC function and stiffness subscales; Lequesne index</p> <p>Joint space loss: minimum joint space width, joint space narrowing $> 5 \text{ mm}$, other structural modifications</p> <p>Adverse events: withdrawal rates and reason for drop-out, adverse events, routine laboratory tests</p> <p>Other: paracetamol consumption</p> <p>Assessment: quarterly assessment of symptoms; radiographs and safety laboratory tests at end of each year</p> <p>Note: in patients with bilateral disease, the target knee was the one more severely affected</p>	<p>Method of randomisation: described, adequate</p> <p>Allocation concealed? Yes</p> <p>Participants blinded? Yes</p> <p>Outcome assessors blinded? Yes</p> <p>Proportion of participants excluded/lost to follow-up: intervention: 35% withdrawals; control: 46% withdrawals; no significant difference in rates or reasons</p> <p>Handling of missing data: worst case analysis and random sampling analysis</p> <p>Intention-to-treat analysis performed? Yes</p> <p>Statistical analysis appropriate? Yes</p> <p>Groups comparable at baseline? Yes</p>

Study	Design	Participants	Interventions	Outcome measures	Quality
Reginster 2001 ⁷⁶ Belgium	<p>Focus: effect of glucosamine sulphate on long-term progression of OA joint structure changes and symptoms</p> <p>Single centre</p> <p>Duration: 3 years</p> <p>Follow-up: no post-intervention follow-up</p> <p>Setting: outpatient</p> <p>Funding: Rotta Research Group (Italy)</p>	<p>Total number: 212</p> <p>Intervention: $n = 106$; 68 completed trial</p> <p>Control: $n = 106$; 71 completed trial</p> <p>Inclusion criteria: > 50 years, primary knee OA of medial femorotibial compartment, diagnosed according to clinical and radiological criteria of ACR</p> <p>Exclusion criteria: history or active presence of rheumatic diseases that could be cause of secondary knee OA; severe articular inflammation; traumatic knee lesions; BMI > 30 kg/m²; substantial abnormalities in haematological, hepatic, renal or metabolic functions; intra-articular or systematic corticosteroids within 3 months preceding enrolment</p> <p>Age: intervention: 66.0 years, SD 8.1; control: 65.5 years, SD 7.5</p> <p>Gender: intervention: 75% female; control: 78% female</p> <p>BMI: intervention: 27.3 kg/m², SD 2.6; control: 27.4 kg/m², SD 2.7</p> <p>OA stage: intervention: 71% K–L grade 2, 29% grade 3; control: 70% K–L grade 2, 30% grade 3</p> <p>OA duration: intervention: 8.0 years, SD 7.5; control: 7.6 years, SD 7.5</p> <p>Comorbidities: not reported</p> <p>Subgroups: highest vs lowest quartile for joint space width (see Bruyere 2003²¹⁵)</p>	<p>Intervention: 1500 mg/day glucosamine sulphate (powder for oral solution) (Rotta)</p> <p>Control: placebo (no details)</p> <p>Co-interventions/rescue analgesia: paracetamol (500 mg tablets) or NSAIDs (diclofenac 50 mg tablets, piroxicam 20 mg capsules or proglumetacin 150 mg tablets); washout before symptom assessment (at least five half-lives of selected medication allowed)</p> <p>Rescue analgesia use: no significant difference in consumption of rescue medication between groups</p> <p>Adherence assessment: over 70% drug intake in 81–91% without significant difference between groups</p>	<p>Primary: mean joint space width of medial compartment of tibiofemoral joint, total WOMAC score</p> <p>Pain: WOMAC joint pain subscale</p> <p>WOMAC: reported</p> <p>Function: WOMAC function and stiffness subscales</p> <p>Joint space loss: mean, minimum joint space width</p> <p>Adverse events: adverse events, routine laboratory tests, fasting glucose</p> <p>Other: use of rescue medication</p> <p>Assessment: radiographs taken at baseline, 1 and 3 years</p>	<p>Method of randomisation: described, adequate</p> <p>Allocation concealed? Yes</p> <p>Participants blinded? Yes</p> <p>Outcome assessors blinded? Yes</p> <p>Proportion of participants excluded/lost to follow-up: intervention: 33% withdrawals; control: 36% withdrawals; no significant difference in rates or reasons</p> <p>Handling of missing data: 3 approaches – (i) worst scenario analysis, (ii) last observation carried forward, (iii) random sampling approach</p> <p>Intention-to-treat analysis performed? Yes</p> <p>Statistical analysis appropriate? Yes</p> <p>Groups comparable at baseline? Yes</p>

continued

TABLE 10 Characteristics of randomised controlled trials fulfilling the inclusion criteria of this review (continued)

Study	Design	Participants	Interventions	Outcome measures	Quality
Chondroitin Michel 2005 ¹⁰⁸ Switzerland	<p>Focus: effect of chondroitin sulphate on cartilage loss in knee OA</p> <p>Single centre</p> <p>Duration: 2 years</p> <p>Follow-up: no post-intervention follow-up</p> <p>Setting: outpatient clinic</p> <p>Funding: unclear</p>	<p>Total number: 300</p> <p>Intervention: <i>n</i> = 150; 110 completed trial</p> <p>Control: <i>n</i> = 150; 109 completed trial</p> <p>Inclusion criteria: 40–85 years, clinically symptomatic knee OA (knee pain while standing, walking, and/or motion for at least 25 of the 30 days prior to study entry, no required minimum level of pain on day of entry); diagnosed according to ACR clinical and radiographic criteria for knee OA; patients with K–L grade 1, 2, 3; target knee defined as the most symptomatic knee on study entrance</p> <p>Exclusion criteria: presence of any causes of secondary knee OA, traumatic knee lesions, severe comorbidity (especially severe heart, renal, lung or neurological disease), previous joint surgery, intra-articular medications including corticosteroids in past month, foreseeable prospect of major surgery during 2-year study period; washout period of 3 months required for potentially longer-acting substances, e.g. glucosamine and chondroitin sulphate</p> <p>Age (mean): intervention: 62.5 years, SD 9.1; control: 63.1 years, SD 10.7</p> <p>Gender: intervention: 51% female; control: 52% female</p> <p>BMI: intervention: 27.7 kg/m², SD 5.2; control: 28.1 kg/m², SD 5.5</p> <p>OA stage/severity: not reported (stated that K–L scores were not significantly different between groups)</p>	<p>Intervention: 800 mg tablet Condrosulf® (IBSA, Hungary) (chondroitins 4- and 6-sulphate) daily</p> <p>Control: identical placebo tablet</p> <p>Co-interventions/rescue analgesia: paracetamol 500 mg tablets at maximum dose of 3 g/day allowed as rescue analgesia; for secondary rescue, NSAIDs were allowed up to a maximum period of 5 consecutive days if primary rescue analgesia with paracetamol was insufficient; physical therapy limited to application of warmth and strengthening exercises when deemed necessary by patient; no other interventions allowed, including steroid injections</p> <p>Rescue analgesia use: similar amounts taken, no details</p> <p>Adherence assessment: pill counts and 12- and 24-month visits; 69% in chondroitin group and 72% in placebo group took more than 70% of tablets during trial (no significant difference between groups)</p>	<p>Primary: minimum and mean joint space width of more severely affected compartment of target knee</p> <p>Pain: WOMAC joint pain subscale</p> <p>WOMAC: reported</p> <p>Function: WOMAC function subscale</p> <p>Joint space loss: joint space narrowing in mm; minimum and mean joint space width measured using digitised radiographs and an image analysis system</p> <p>Adverse events: reported</p> <p>Other: none</p> <p>Assessment: follow-up assessments conducted by mail every 3 months over 2-year study period (WOMAC and treatment diaries); radiographs at baseline and 24 months; clinical examination and routine laboratory tests at baseline, 12 and 24 months</p>	<p>Method of randomisation: described, adequate</p> <p>Allocation concealed? Yes</p> <p>Participants blinded? Yes</p> <p>Outcome assessors blinded? Yes</p> <p>Proportion of participants excluded/lost to follow-up: 27% in each study group; no significant difference in reasons for withdrawal</p> <p>Handling of missing data: data at last visit used; radiographic evaluation done at time of drop-out of patients who dropped out (except for 16 patients who dropped out within 1 month of study entry)</p> <p>Intention-to-treat analysis performed? Yes</p> <p>Statistical analysis appropriate? No measures of variability reported</p> <p>Groups comparable at baseline? Yes</p>

Study	Design	Participants	Interventions	Outcome measures	Quality
Uebelhart 1998 ¹⁴ Switzerland	Focus: clinical, radiological, biological efficacy and tolerability of chondroitin 4- and 6-sulphate in knee OA Single centre Duration: 1 year Follow-up: no post-intervention follow-up Setting: in- or outpatient Funding: IBSA (producer)	OA duration: not reported Comorbidities: not reported Subgroups: for joint space changes, all patients ($n = 300$) versus patients with minimum joint space ≥ 1 mm at entry ($n = 225$) Total number: 46 Intervention: $n = 23$; 21 completed trial Control: $n = 23$; 21 completed trial Inclusion criteria: 35–78 years, mono- or bilateral clinically symptomatic knee OA with a minimum remaining femorotibial joint space of 25% on standard X-ray Exclusion criteria: patients with inflammatory or systemic diseases or other conditions involving joints, lower limbs axial deviation $> 5^\circ$, steroids or bone-oriented treatments < 3 months before study began Age: intervention: 60 years, SD 13; control: 57 years, SD 11 Gender: intervention: 48% female; control: 56% female Weight: intervention: 72 kg, SD 11; control: 76 kg, SD 14 OA stage: intervention: 43% K–L grade 1, 48% grade 2, 9% grade 3; control: 48% K–L grade 1, 43% grade 2, 9% grade 3 OA duration: not reported Comorbidities: not reported Subgroups: none	Intervention: 800 mg/day chondroitin 4- and 6-sulphate (Chondrosulf, two sachets of 400 mg, dissolved in half a glass of water) Control: same daily amount of vehicle alone Co-interventions/rescue analgesia: free access to paracetamol as rescue medication Rescue analgesia use: analgesic consumption not reported	Primary: spontaneous joint pain (Huskisson VAS), overall mobility capacity (VAS) Pain: Huskisson VAS WOMAC: no Function: mobility capacity (VAS) Joint space loss: joint space measurement Adverse events: tolerability Other: bone joint metabolism Assessment: at entry and 3, 6, and 12 months; X-rays at entry and 12 months Note: only the most damaged knee was taken into account for inclusion and follow-up	Method of randomisation: method not described Allocation concealed? Unclear Participants blinded? Yes Outcome assessors blinded? Yes for joint space measurements; other measurements unclear Proportion of participants excluded/lost to follow-up: 8.7% in both comparison groups; chondroitin group: 1 death, 1 left the country; placebo group: 1 left the country, 1 not satisfied Handling of missing data: not described Intention-to-treat analysis performed? Unclear (probably not) Statistical analysis appropriate? Yes Groups comparable at baseline? Yes

continued

TABLE 10 Characteristics of randomised controlled trials fulfilling the inclusion criteria of this review (continued)

Study	Design	Participants	Interventions	Outcome measures	Quality
Uebelhart 2004 ¹¹⁶ Switzerland/Belgium/ France/Italy	<p>Focus: efficacy of a 3-month, twice a year intermittent treatment with chondroitin sulphate in knee OA</p> <p>Multicentre</p> <p>Duration: 1 year</p> <p>Follow-up: no post-intervention follow-up</p> <p>Setting: not reported</p> <p>Funding: IBSA (producer)</p>	<p>Total number: 110</p> <p>Intervention: n = 54; 43 completed trial</p> <p>Control: n = 56; 41 completed trial</p> <p>Inclusion criteria: age 40 or over, mono- or bilateral clinically symptomatic idiopathic knee OA according to ACR criteria; patients with K-L score 1–3, with a minimum 25% remaining medial femorotibial joint space upon entry</p> <p>Exclusion criteria: other inflammatory joint diseases or other systemic conditions affecting or involving joints; neoplasias, bone metabolic diseases and/or other metabolic and systemic diseases; treatments such as intra-articular steroids, NSAIDs, symptom-modifying agents or bone-oriented therapies (e.g. fluorides, bisphosphonates, calcitonin, hormonal substitution within 3 months before beginning of study)</p> <p>Age: intervention: 63.2 years, SD 9.1; control: 63.7 years, SD 8.1</p> <p>Gender: intervention: 80% female; control: 82% female</p> <p>Weight: intervention: 76.8 kg, SD 15.8; control: 76.4 kg, SD 13.8</p> <p>OA stage: intervention: 13% K-L grade 1, 59% grade 2, 28% grade 3; control: 11% K-L grade 1, 59% grade 2, 30% grade 3</p> <p>OA duration: intervention: 50.1 months; control: 52.4 months</p> <p>Comorbidities: not reported</p> <p>Subgroups: none</p>	<p>Intervention: 800 mg/day chondroitin 4- and 6-sulphate (Condrosulf sachets taken with a glass of water); treatment administered intermittently from months 6 and 9</p> <p>Control: identical sachets with vehicle only</p> <p>Co-interventions/rescue analgesia: medications as listed in exclusion criteria not allowed; paracetamol up to 4 g/day allowed; paracetamol treatment stopped 24 hours prior to each visit</p> <p>Rescue analgesia use: after first month, paracetamol consumption significantly greater in placebo group (at 12 months 55.5 tablets, SD 68.1 versus 25.8, SD 37.0 in placebo group)</p> <p>Adherence assessment: adherence 93–98%, no significant difference between groups</p>	<p>Primary: Lequesne index</p> <p>Pain: spontaneous joint pain (Huskisson VAS)</p> <p>WOMAC: no</p> <p>Function: 20 m walking time</p> <p>Joint space loss: joint space surface area, mean and minimum joint space width</p> <p>Adverse events: adverse events, clinical laboratory evaluation</p> <p>Other: global patient and physician assessment; paracetamol consumption</p> <p>Note: in patients with bilateral knee OA, the most symptomatic knee was selected as the study target knee</p> <p>Assessment: every 3 months; radiographs at entry and 12 months</p>	<p>Method of randomisation: described, adequate</p> <p>Allocation concealed? Yes</p> <p>Participants blinded? Yes</p> <p>Outcome assessors blinded? Yes</p> <p>Proportion of participants excluded/lost to follow-up: 10 patients (of 120) not included in intention-to-treat population (did not turn up for second visit, did not take any medication); 11 drop-outs in intervention and 15 in placebo group; no significant difference</p> <p>Handling of missing data: last observation carried forward</p> <p>Intention-to-treat analysis performed? Yes</p> <p>Statistical analysis appropriate? Yes</p> <p>Groups comparable at baseline? Yes</p>

Study	Design	Participants	Interventions	Outcome measures	Quality
Glucosamine/chondroitin Messier 2007 ¹²² USA	Focus: effect of glucosamine hydrochloride plus chondroitin sulphate alone and combined with exercise on physical function, pain, strength, balance and mobility in older adults with knee OA Single centre Duration: 1 year Follow-up: no post-intervention follow-up Setting: outpatient clinical research centre Funding: Rexall Sundown Inc.	Total number: 89 Intervention: n = 45; 37 completed trial Control: n = 44; 35 completed trial Inclusion criteria: ≥ 50 years, radiographic evidence of mild to moderate knee OA (K-L grades 2-3) who met ACR classification criteria Exclusion criteria: currently participating in another trial, dementia, active cancer other than skin cancer, anaemia, severe renal insufficiency, hepatic diseases, excess alcohol use, knee-joint replacement, inability to walk unassisted at least 128 m in 6 minutes, completion of more than 20 minutes of formal exercise per week during past 3 months, planned absence for longer than 3 weeks during required study visits, residing further than 1 hour drive from research facilities, shellfish allergy, exposure to glucosamine/chondroitin in 6 months prior to randomisation, unwilling to discontinue current arthritis medication during 2-week washout and 12-month intervention period (other than rescue medication), less than 80% compliance during run-in period, failure to complete graded exercise test, required human assistance with activities related to knee pain, recent knee surgeries or knee injections, e.g. cortisone and hyaluronic acid Age: intervention: 70.0 years, SE 1.28; control: 74.1 years, SE 1.32; p = 0.03 Gender: intervention: 75.6% female; control: 65.9% female	Intervention: 1500/1200 mg glucosamine hydrochloride plus chondroitin sulphate (GH/CS); choice of 1 × or 3 × a day regimen; 6 healthy lifestyle classes; after 6-month exercise programme (1 hour twice a week) added for last 6 months (combined facility and home-based exercise programme, two 15-minute walking sessions, separated by 20 minutes of strength training) Control: placebo of identical size, colour, shape, regimen; lifestyle classes and exercise programme after 6 months as in GH/CS group Co-interventions/rescue analgesia: paracetamol maximum dosage 4 g/day Rescue analgesia use: decrease in paracetamol use by 12 months of 37% in intervention and 11% in placebo group (not stated if significant) Run-in/washout period: 2 weeks before start of intervention; discontinuation of all medications; rescue medications/required medication unrelated to OA permitted; unblinded placebo supply (3 pills/day, compliance assessed) Adherence assessment: 91–97%	Primary: WOMAC function Pain: WOMAC pain subscale WOMAC: yes Function: WOMAC function subscale; mobility (distance walked in 6 minutes) Joint space loss: not assessed Adverse events: not systematically reported Other: knee concentric extension and flexion strength (Kin-Com 125E isokinetic dynamometer); balance (AMTI force platform) Assessment: screening visit, baseline, 6 and 12 months	Method of randomisation: not explicitly described, computer allocation implied Allocation concealed? Yes Participants blinded? Yes Outcome assessors blinded? Yes Proportion of participants excluded/lost to follow-up: intervention: 18% withdrawals; control: 20% withdrawals; not reported if significant differences between groups Handling of missing data: last observation carried forward Intention-to-treat analysis performed? Yes Statistical analysis appropriate? Yes Groups comparable at baseline? No, GH/CS were significantly younger, more overweight, and had a higher income than placebo group

continued

TABLE 10 Characteristics of randomised controlled trials fulfilling the inclusion criteria of this review (continued)

Study	Design	Participants	Interventions	Outcome measures	Quality
Rai 2004 ²⁰ India	Focus: effect of chondroitin plus glucosamine sulphate on joint structure and symptoms in knee OA Single centre Duration: 1 year Follow-up: no post-intervention follow-up Setting: orthopaedic outpatient centre Funding: unclear	BMI: intervention: 30.7 kg/m ² , SE 0.93; control: 27.3 kg/m ² , SE 0.71; <i>p</i> = 0.005 OA stage/severity/duration: not reported Comorbidities: listed in detail, no significant difference between groups Total number: 100 Intervention: <i>n</i> = 50 Control: <i>n</i> = 50 Inclusion criteria: > 50 years, primary knee OA mainly of medial femorotibial compartment diagnosed according to clinical and radiological criteria of ACR Exclusion criteria: history or active presence of other rheumatic diseases responsible for secondary OA, severe articular inflammation as confirmed by physical examination, K-L grade 4, Lequesne index higher than 12, history of intra-articular injection or systemic steroid intake in 3 months preceding enrolment Age: intervention: 54.7 years; control: 53.9 years Gender: not reported Weight: intervention: 69.1 kg; control: 68.9 kg OA stage/severity: no details, stated that OA was comparable at baseline and mild to moderate OA duration: not reported Comorbidities: not reported Subgroups: none	Intervention: oral combination of glucosamine sulphate and chondroitin sulphate (Kondro [®] , capsule) (Panacea Biotech Ltd, India) – dosing not stated, presumably one capsule a day; Kondro contains 250 mg glucosamine sulphate and 200 mg chondroitin sulphate Control: matching placebo capsules Co-interventions/rescue analgesia: patients advised to take paracetamol for pain Rescue analgesia use: differences between groups not reported	Primary: joint space width changes in narrowest medial compartment of tibiofemoral joint Pain: no separate assessment WOMAC: no Function: Lequesne index Joint space loss: minimum joint space width Adverse events: not reported Other: none Assessment: every 4 weeks; standardised radiographs at enrolment and after 1 year	Method of randomisation: not reported Allocation concealed? Unclear Participants blinded? Yes, described as double blind Outcome assessors blinded? Yes, described as double blind Proportion of participants excluded/lost to follow-up: not reported Handling of missing data: not reported Intention-to-treat analysis performed? Not reported Statistical analysis appropriate? Yes Groups comparable at baseline? Yes

ACR, American College of Rheumatology; BMI, body mass index; K-L, Kellgren and Lawrence scores; NSAID(s), non-steroidal anti-inflammatory drug(s); NTX, terminal type I collagen telopeptides; VAS, visual analogue scale.

Kawasaki which just stated that both Kellgren–Lawrence grades 2 and 3 were included). In all trials, baseline characteristics were well balanced in the comparison groups.

Interventions

In the Pavelká and Reginster trials, 1500 mg per day glucosamine sulphate (Rotta) was given as a powder oral solution. Kawasaki used 1500 mg per day glucosamine hydrochloride. All trials reported that there was no significant difference in rescue analgesia use between comparison groups and that medication adherence was good.

Outcome measures and further trial details are summarised in *Table 10*.

Trial quality

Details for trial quality are shown in *Table 10*. Trial quality for the trials by Pavelká and Reginster was good. The trial by Kawasaki was of poor quality. Randomisation and allocation concealment were not described and there was no blinding (with the exception of assessment of joint space width).

Results

Structure Table 11 summarises the results for trials of glucosamine on joint structure.

The trials by Pavelká and Reginster showed a statistically significant effect in favour of glucosamine for minimum joint space width, with a weighted mean difference from baseline to

TABLE 11 Results for trials of glucosamine on joint structure

Study	Outcome	No. of participants	Baseline	Change from baseline/ difference between groups	p-value (between groups)
Kawasaki 2008 ¹²³ (Hydrochloride)	Joint space width	I: n = 49 C: n = 42	I: 2.6 mm, SD 1.2 C: 3.1 mm, SD 1.0	Change from baseline: I: 0.0 mm (95% CI –2.2 to 1.7) C: –0.3 mm (95% CI –1.8 to 1.6) Difference: 0.2 mm	NS
Pavelká 2002 ⁷⁷ (Sulphate)	Minimum joint space width	I: n = 101 C: n = 101	I: 3.89 mm, SD 1.48 C: 3.63 mm, SD 1.57	Change from baseline: I: +0.04 mm (95% CI –0.06 to 0.14) C: –0.19 mm (95% CI –0.29 to –0.09) Difference: 0.23 mm (95% CI 0.09 to 0.37)	0.001
	Severe joint space narrowing (> 0.5 mm)			End of study: I: n = 5 C: n = 14 NNT = 11	0.05
Reginster 2001 ⁷⁶ (Sulphate)	Mean joint space width	I: n = 106 C: n = 106	Total joint space width: I: 5.23 mm, SD 1.36 C: 5.39 mm, SD 1.29	Change from baseline: I: –0.06 mm (95% CI –0.22 to 0.09) C: –0.31 mm (95% CI –0.48 to –0.13) Difference: 0.24 mm (95% CI 0.01 to 0.48)	0.043
	Minimum joint space width	I: n = 106 C: n = 106	I: 3.82, SD 1.32 mm C: 3.95, SD 1.24 mm	Change from baseline: I: –0.07 mm (95% CI –0.22 to 0.07) C: –0.40 mm (95% CI –0.56 to –0.24) Difference: 0.33 mm (95% CI 0.12 to 0.54)	0.003

C, control; I, intervention; NNT, number needed to treat; NS, not significant.

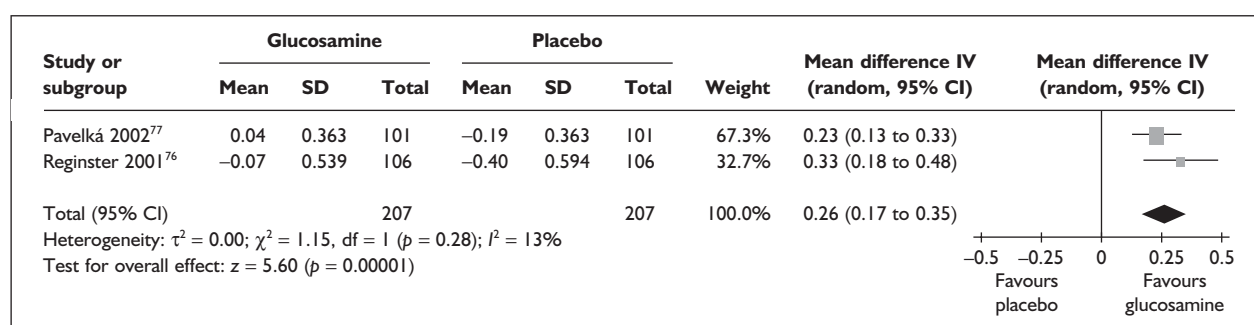


FIGURE 3 Glucosamine sulphate: a meta-analysis of minimum joint space width – difference from baseline (fixed-effects model produces same point estimate; random-effects model presented as confidence interval better reflects the uncertainty around that point estimate). IV, inverse difference.

end of study of 0.26 mm (95% CI 0.17 to 0.35), indicating less joint space loss with glucosamine (Figure 3). Both trials reported a point estimate in favour of glucosamine sulphate, with minimal evidence of heterogeneity in the size of the effect being observed. Pavelká found significantly more patients with severe joint space narrowing (more than 0.5 mm) in the placebo group than in the intervention group ($n = 14$ versus $n = 5$, $p < 0.05$).

Mean joint space width was reported by Reginster only, who observed a significant difference of 0.24 mm (95% CI 0.01 to 0.48) in mean joint space narrowing, indicating a preservation of joint space with glucosamine. Kawasaki reported results for joint space width (determined at the centre point of the medial femoral condyle) and found no significant effect of glucosamine hydrochloride versus control.

A subgroup analysis of the Reginster trial (Table 12) compared patients in the lowest quartile for mean joint space width (joint space width < 4.5 mm) with patients in the highest quartile for mean joint space width (joint space width > 6.2 mm). In the patients in the lowest quartile ($n = 29$ intervention, $n = 23$ control), mean joint space width increased by 0.22 mm (SD 0.66 mm) in the intervention group and 0.13 mm (SD 0.81 mm) in the control group (no statistically significant difference). In the patients in the highest quartile ($n = 27$ intervention, $n = 26$ control), mean joint space width decreased by 0.45 mm (SD 1.04 mm) in the intervention group and by 1.05 mm (SD 1.28 mm) in the control group (difference not statistically significant, $p = 0.1$). There was a statistically significant difference in joint space change between the two subgroups ($p < 0.01$). The authors speculated that the results may indicate that patients with less severe disease may benefit more from structure-modifying drugs, although

improvements in the joint space width were also observed in the control group.

Symptoms/pain For function and pain assessment, the trials did not report data consistently (for example, Pavelká and Kawasaki reported WOMAC scores as points, whereas Reginster used per cent change on a VAS), only Pavelká used the Lequesne index, and Kawasaki used the Japan Orthopaedic Association (JOA) score and a visual analogue pain scale, so data could not be summarised in a meta-analysis (Table 13).

Pain Pavelká found a statistically significant effect in favour of glucosamine compared with placebo at the end of the 3-year trial for the WOMAC pain subscale [difference between groups 0.7 points (95% CI 0.06 to 1.3)]. Similarly, Reginster found a statistically significant effect in favour of glucosamine for the WOMAC pain subscale [change from baseline approximately -36.7 , SE 8.3 mm (VAS) for glucosamine and -7.5 SE, 10.6 mm for the control group (estimated from graph)]. Kawasaki did not find any statistically significant difference in the WOMAC pain subscale or the VAS pain scale between the glucosamine hydrochloride and control groups. Meta-analysis (Figure 4) illustrates the small, but statistically significant favourable effect for glucosamine.

Little detail was reported in the three trials about the use of rescue analgesia with the exception of stating in all three trials that there was no statistically significant difference in the volume of rescue analgesia used.

Function Pavelká found a statistically significant effect in favour of glucosamine compared with placebo for both the WOMAC function and stiffness subscales (difference between groups 2.1 points (95% CI 0.28 to 3.9) for function and

TABLE 12 Subgroup analysis: summary from Reginster 2001 trial⁷⁶

Study	Subgroup	Outcome	Change from baseline/ difference between groups	p-value
Reginster 2001 ⁷⁶	Mean joint space width lowest quartile (< 4.5 mm, n = 29 intervention, n = 23 control)	Change in mean joint space width	Joint space width < 4.5 mm: I: +6.2%, SD 17.5; +0.22 mm, SD 0.66	< 0.01 for joint space change between the two quartiles
	vs Highest quartile (> 6.2 mm, n = 27 intervention, n = 26 control)		C: +3.8%, SD 23.8; +0.13 mm, SD 0.81 Joint space width > 6.2 mm: I: -6.0%, SD 15.1; -0.45 mm, SD 1.04 C: -14.9%, SD 17.9; -1.05 mm, SD 1.28	
C, control; I, intervention.				

TABLE 13 Summary of glucosamine trial results for pain, function and composite health state scores

Study	No. of participants	Outcome	Baseline	Change from baseline/difference between groups	p-value
Kawasaki 2008 ¹²³	I: n = 49 C: n = 42	JOA total score (range 0–100)	I: 74.2, SD 13.3 C: 69.6, SD 14.4	I: +13.7 (95% CI -18.5 to 43) C: +16.3 (95% CI -4.8 to 39.8)	NS
		JOA gait (range 0–30)	I: 23.3, SD 5.5 C: 21.5 SD 6.6	I: +4.4 (95% CI 2.8 to 11) C: +6.3 (95% CI -3.6 to 20)	NS
	JOA stairs (range 0–25)	I: 14.7, SD 5.6 C: 11.9, SD 6.1	I: +5.5 (95% CI -8.2 to 20.3) C: +6.3 (95% CI -1.1 to 17.5)	NS	
	JOA range of motion (range 0–35)	I: 29.4, SD 5.0 C: 29.5, SD 4.8	I: +1.4 (95% CI -5.5 to 5.5) C: +1.9 (95% CI -6.1 to 10)	NS	
	JOA swelling (range 0–10)	I: 6.8, SD 2.7 C: 6.7, SD 3.3	I: +2.6 (95% CI -0.3 to 5) C: +1.9 (95% CI -5.0 to 10)	NS	
	VAS pain (range 0–10)	I: 5.0, SD 2.0 C: 4.9, SD 1.8	I: -1.6 (95% CI -5.0 to 2.2) C: -1.7 (95% CI -5.5 to 2.5)	NS	
	WOMAC total (range 0–96)	I: 31.5, SD 15.6 C: 28.7, SD 16.0	I: -14.9 (95% CI -45.5 to 6) C: -11.5 (95% CI -38.8 to 7.5)	NS	
	WOMAC pain (range 0–20)	I: 7.2, SD 3.9 C: 6.5, SD 3.4	I: -3.6 (95% CI -14.1 to 3) C: -2.9 (95% CI -9.5 to 0.5)	NS	
	WOMAC stiffness (range 0–8)	I: 3.4, SD 1.6 C: 2.7, SD 1.6	I: -1.5 (95% CI -5.1 to 1.0) C: -0.7 (95% CI -3 to 1.5)	NS	
	WOMAC function (range 0–68)	I: 20.8, SD 11.0 C: 19.6, SD 11.5	I: -9.8 (95% CI -31.2 to 5.2) C: -7.5 (95% CI -27.2 to 7)	NS	
<i>continued</i>					

TABLE 13 Summary of glucosamine trial results for pain, function and composite health state scores (continued)

Study	No. of participants	Outcome	Baseline	Change from baseline/difference between groups	p-value
Pavelká 2002 ⁷⁷	I: n = 101 C: n = 101	Lequesne index (points)	I: 8.95, SD 2.30 C: 8.94, SD 2.27	Change from baseline: I: -1.7 (95% CI -2.2 to -1.2) C: -0.82 (95% CI -1.1 to -0.51) Difference: 0.91 (95% CI 0.34 to 1.5)	0.002
		WOMAC total (points)	I: 30.70, SD 14.40 C: 30.48, SD 14.43	Change from baseline: I: -8.0 (95% CI -9.8 to -6.3) C: -4.9 (95% CI -6.5 to 3.2) Difference: 3.1 (95% CI 0.77 to 5.5)	0.01
		WOMAC pain (points)	I: 6.61, SD 3.45 C: 6.33, SD 3.13	Change from baseline: I: -2.0 (95% CI -2.4 to -1.5) C: -1.3 (95% CI -1.7 to 0.88) Difference: 0.7 (95% CI 0.06 to 1.3)	0.03
		WOMAC function (points)	I: 21.84, SD 10.67 C: 22.00, SD 11.03	Change from baseline: I: -5.8 (95% CI -7.1 to -4.4) C: -3.7 (95% CI -4.9 to -2.5) Difference: 2.1 (95% CI 0.28 to 3.9)	0.02
		WOMAC stiffness (points)	I: 2.25, SD 1.47 C: 2.15, SD 1.44	Change from baseline: I: -0.31 (95% CI -0.55 to 0.07) C: +0.11 (95% CI -0.12 to 0.34) Difference: 0.42 (95% CI 0.09 to 0.75)	0.01
Reginster 2001 ⁷⁶	I: n = 106 C: n = 106	WOMAC total (out of 2400mm)	I: 1030.2mm, SD 473.8 C: 939.7mm, SD 484.8	Change from baseline: I: -11.7% (95% CI -20.3 to -3.2) C: +9.8% (95% CI -6.2 to 25.8) Difference: 21.6% (95% CI 3.5 to 39.6)	0.020
		WOMAC pain	I: 194.1 mm, SD 101.9 C: 172.2mm, SD 104.5	Change from baseline: I: ~-36.7mm, SE 8.3 C: ~-7.5mm, SE 10.6 (estimated from graph)	0.047
		WOMAC function	I: 740.1 mm, SD 364.2 C: 670.8mm, SD 367.8	Change from baseline: I: ~-160mm, SE 24.2 C: ~-65.5mm, SE 31.5 (estimated from graph)	0.020
		WOMAC stiffness	I: 96.0mm, SD 54.8 C: 96.7mm, SD 54.6		NS

C, control; I, intervention, NS, not significant.

0.42 points (95% CI 0.09 to 0.75) for stiffness). Reginster found statistically significant effects in favour of glucosamine for the WOMAC function subscale [change from baseline about -160 SE, 24.2 mm (VAS) for glucosamine and -65.5, SE 31.5 mm for the control group (estimated from graph)], but not for the stiffness subscale. Kawasaki did not find any statistically significant

difference in the JOA total score or the gait, stairs, range of motion or swelling subscores, or in the WOMAC stiffness and function subscores between glucosamine hydrochloride and the control group. Meta-analysis (Figure 5) illustrates the small, but statistically significant favourable effect for glucosamine. While the CIs overlap, visual inspection identifies substantial heterogeneity,

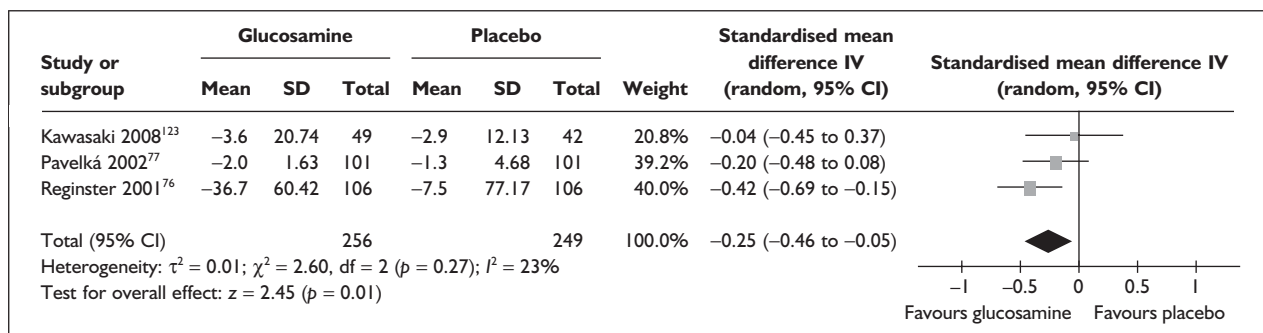


FIGURE 4 Glucosamine sulphate and hydrochloride: a meta-analysis of WOMAC pain scores at end of study (fixed-effects model produces same point estimate; random-effects model presented as confidence interval better reflects the uncertainty around that point estimate). IV, inverse difference.

with the glucosamine hydrochloride product demonstrating little evidence of an effect.

Function/pain composite scores Pavelká found a statistically significant effect in favour of glucosamine compared with placebo for both the Lequesne index and the WOMAC total score (difference between groups 0.91 points (95% CI 0.34 to 1.5) for the Lequesne index and 3.1 (95% CI 0.77 to 5.5) for the WOMAC total score). Reginster found statistically significant effects in favour of glucosamine for the WOMAC total score [per cent change from baseline, difference between groups 21.6% (95% CI 3.5 to 39.6)]. Kawasaki did not find any significant difference in the WOMAC total score between glucosamine hydrochloride and the control group.

Knee arthroplasty In a follow-up analysis⁵² of the trials by Reginster and Pavelká taken together, patients with at least 12 months of treatment were followed up for their joint replacement status. Of 340 eligible patients, 275 (81%) could be followed up. Of these, 144 had been in the glucosamine groups of the trials and 131 had been in the placebo groups. No significant baseline differences

were found between the patients followed up and those lost to follow-up. After a mean post-intervention follow-up of 5 years (8 years from trial baseline), significantly fewer patients in the former glucosamine groups had received knee arthroplasty than patients in the former placebo groups (9/144 in the glucosamine groups and 19/131 in the placebo groups, RR 0.43 (95% CI 0.20 to 0.92, $p = 0.024$).

Adverse events Neither Pavelká nor Reginster found significant differences in reported adverse effects between the glucosamine groups and the placebo groups. No significant differences in routine laboratory test results were seen, and Reginster did not note any change in glucose homeostasis. Adverse events were not reported systematically in the study by Kawasaki. One patient in the glucosamine group and two in the control group withdrew from the trial because of adverse events.

Chondroitin

Trial characteristics

Of the three chondroitin trials, all were described as double-blind, placebo-controlled RCTs. The trial by Michel¹⁰⁸ had a duration of 2 years, whereas the

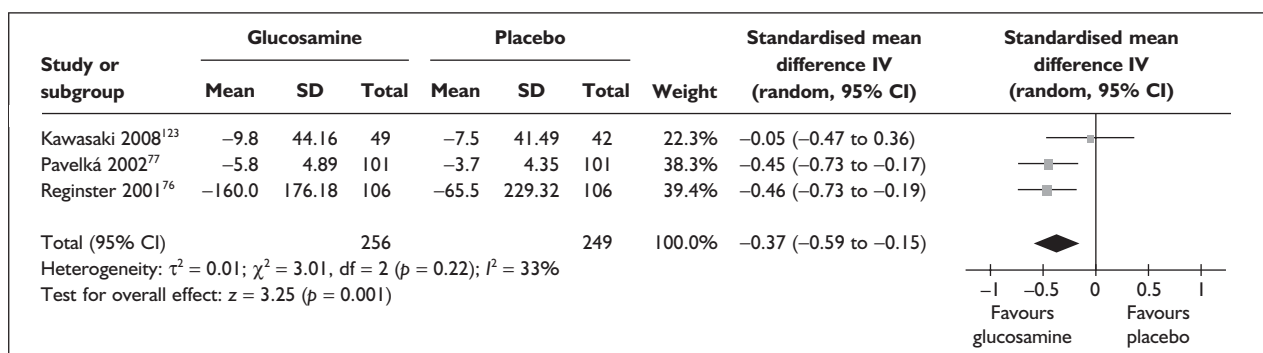


FIGURE 5 Glucosamine sulphate and hydrochloride: a meta-analysis of WOMAC function scores at end of study (fixed-effects model produces same point estimate; random-effects model presented as confidence interval better reflects the uncertainty around that point estimate). IV, inverse difference.

two trials by Uebelhart^{114,116} had a duration of 1 year. The two trials by Uebelhart^{114,116} were industry funded. No funding information was available for the trial by Michel.¹⁰⁸

A total of 456 people participated in the three trials. The trials included participants of a mean age of between 57 and 64 years, with between 48% and 82% being female. Osteoarthritis severity was not reported in the trial by Michel; in the trials by Uebelhart, between 13% and 48% had OA of Kellgren–Lawrence grade 1 at baseline, between 43% and 59% had grade 2, and between 9% and 30% had grade 3 [with more patients in the Uebelhart (2004) study¹¹⁶ having more severe disease]. In all trials, baseline characteristics were well balanced in the comparison groups.

Interventions

In the trial by Michel, 800 mg/day chondroitins 4- and 6-sulphate [Condrosulf® (IBSA, Hungary)] were given as a tablet. In the trials by Uebelhart (1998)¹¹⁴ and Uebelhart (2004),¹¹⁶ 800 mg/day chondroitins 4- and 6-sulphate (Condrosulf) were given in powder form. In the Michel and Uebelhart (1998) trials the treatment was given continuously, whereas in the trial by Uebelhart (2004) treatment was administered intermittently for 3-month periods (from study entry to the third month, and from the sixth to the ninth months). Michel reported that analgesia use was similar between the comparison groups; no information was given in the trial by Uebelhart (1998), whereas in the trial by Uebelhart (2004) paracetamol consumption was significantly greater in the placebo group at 12 months than in the intervention group.

Outcome measures and further details of the trials are summarised in *Table 10*.

Trial quality

The Michel and Uebelhart (2004) trials were of good quality. The trial by Uebelhart (1998) was of poor quality, reporting little detail of the randomisation procedure and allocation concealment.

Results

Structure *Table 14* summarises the results for chondroitin on structural outcomes.

The three chondroitin trials showed a significant effect in favour of chondroitin for minimum joint space width, with the weighted mean difference changing from 0.02 mm (95% CI –0.20 to 0.24) at baseline to 0.18 mm (95% CI 0.07 to 0.30) at the

end of the trials ($p = 0.001$, random-effects model), no statistically significant heterogeneity, but the estimate was driven by the larger trial by Michel (*Figure 6*). Similarly, a significant effect in favour of chondroitin was shown for mean joint space width, with the weighted mean difference changing from –0.01 mm (95% CI –0.30 to 0.28) at baseline to 0.20 mm (95% CI 0.07 to 0.32) at the end of the trials ($p = 0.003$, random-effects model) (*Figure 7*). These results indicate less joint space loss with chondroitin sulphate. Uebelhart (1998) also found a significant positive effect of chondroitin sulphate compared with placebo on some indicators of bone metabolism.

Michel did a subgroup analysis of the patients with a minimum joint space width of 1 or more millimetres at entry (225/300 patients) and found no significant difference to their main results (*Table 15*). They also state that mean joint space width at baseline had no influence on radiographic progression.

Symptoms/pain Results for function and pain were very mixed and significant changes in joint space were not always mirrored by significant changes in pain/function (*Table 16*).

Pain Michel did not find any significant differences between chondroitin sulphate and placebo for the WOMAC pain subscore. The trials by Uebelhart (1998 and 2004), on the other hand, found a statistically significant effect in favour of chondroitin sulphate for the Huskisson visual analogue pain scale [a decrease of 3.66 cm in the intervention group and 1.64 cm in the placebo group ($p < 0.001$) in Uebelhart (1998) and a decrease of 24.5 mm in the intervention group and 15.3 mm in the placebo group ($p < 0.05$) in Uebelhart (2004)].

Uebelhart (1998) did not report on the use of rescue analgesia but Uebelhart (2004) noted statistically significantly less use of paracetamol in the chondroitin group compared with the placebo group at 12 months (25.8 tablets versus 55 tablets per month; $p < 0.05$). Michel reported no statistically significant difference.

Function Michel did not find any significant differences between chondroitin sulphate and placebo for the WOMAC function or stiffness subscores. The trial by Uebelhart (1998) found no significant effect for overall mobility capacity, but the trial by Uebelhart (2004) found statistically significant results in favour of chondroitin sulphate

TABLE 14 Summary of the effect of chondroitin on joint structure

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)	
Michel 2005 ¹⁰⁸	Minimum joint space width	I: 2.41 mm, SD 0.14 C: 2.35 mm, SD 0.14		Change from baseline: I: +0.045 mm, SD 0.48 (95% CI -0.03 to 0.12) C: -0.07 mm, SD 0.56 (95% CI -0.16 to 0.02) Difference: 0.12 mm, SD 0.52 (95% CI 0.00 to 0.24)	0.05	
		I: 3.04 mm, SD 0.14 C: 3.00 mm, SD 0.15		Change from baseline: I: 0.0 mm, SD 0.53 (95% CI -0.08 to 0.09) C: -0.14 mm, SD 0.61 (95% CI -0.24 to -0.04) Difference: 0.14 mm, SD 0.57 (95% CI 0.01 to 0.27)	0.04	
Uebelhart 1998 ¹¹⁴	Medial femorotibial joint minimum width	I: (n = 14) 0.34 cm, SD 0.10 C: (n = 12) 0.40 cm, SD 0.10	I: (n = 14) 0.35 cm, SD 0.10 C: (n = 12) 0.36 cm, SD 0.13		NS	
		I: (n = 14) 0.44 cm, SD 0.11 C: (n = 12) 0.51 cm, SD 0.10	I: (n = 14) 0.44 cm, SD 0.10 C: (n = 12) 0.46 cm, SD 0.14		< 0.05	
	Medial femorotibial joint surface area	I: (n = 14) 1.08 cm ² , SD 0.32 C: (n = 12) 1.29 cm ² , SD 0.28	I: (n = 14) 1.09 cm ² , SD 0.33 C: (n = 12) 1.17 cm ² , SD 0.36			NS
		Bone metabolism			Significant effect on bone metabolism found: osteocalcin, pyridinoline/creatinine and deoxypyridinoline/creatinine significantly higher; and keratin sulphate significantly lower than in placebo group, <i>p</i> = 0.001	

continued

TABLE 14 Summary of the effect of chondroitin on joint structure (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Uebelhart 2004 ¹¹⁶	Joint surface area	I: 68.0 mm ² , SD 27.2 C: 63.3 mm ² , SD 24.4	I: 67.8 mm ² , SD 26.9 C: 58.7 mm ² , SD 20.9	Change from baseline: I: -0.19 mm ² (95% CI -3.56 to 3.17) C: -4.55 mm ² (95% CI -8.61 to -0.49) Difference: 4.36 mm ² (95% CI -0.19 to 8.91)	NS
	Minimum joint space width	I: 3.65 mm, SD 1.46 C: 3.54 mm, SD 1.39	I: 3.61 mm, SD 1.51 C: 3.23 mm, SD 1.27	Change from baseline: I: -0.04 mm (95% CI -0.23 to 0.14) C: -0.32 mm (95% CI -0.57 to -0.07) Difference: 0.27 mm (95% CI 0.004 to 0.55)	0.047
	Mean joint space width	I: 4.20 mm, SD 1.51 C: 4.03 mm, SD 1.47	I: 4.20 mm, SD 1.58 C: 3.74 mm, SD 1.28	Change from baseline: I: -0.006 mm (95% CI -0.20 to 0.18) C: -0.29 mm (95% CI -0.53 to -0.04) Difference: 0.28 mm (95% CI 0.01 to 0.55)	0.039
C, control; I, intervention; NS, not significant.					

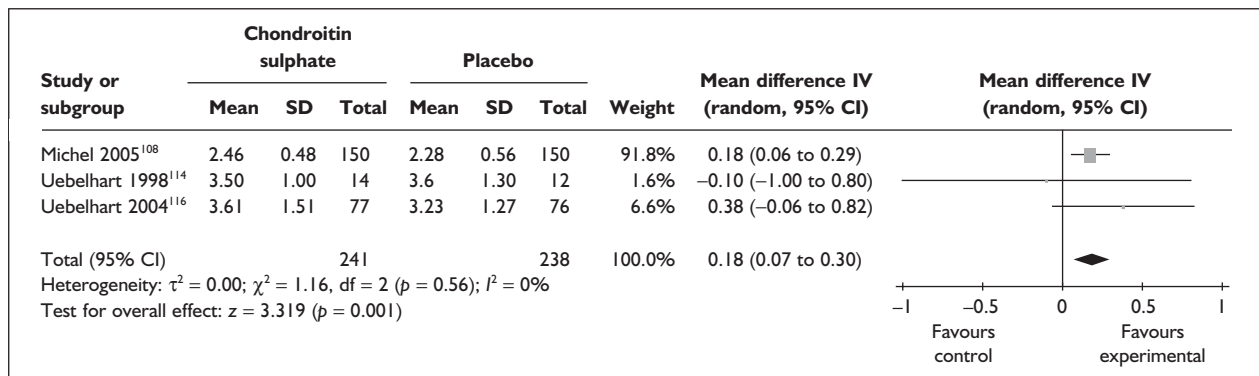


FIGURE 6 Chondroitin sulphate: a meta analysis of minimum joint space width at end of study (fixed-effects model produces same point estimate; random-effects model presented as confidence interval better reflects the uncertainty around that point estimate). IV, inverse difference

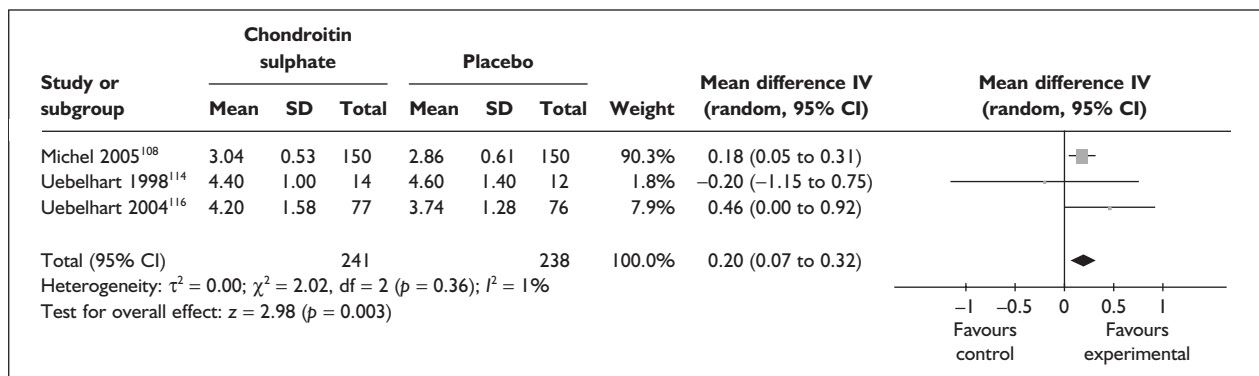


FIGURE 7 Chondroitin sulphate: a meta-analysis of minimum joint space width at end of study (fixed-effects model produces same point estimate; random-effects model presented as confidence interval better reflects the uncertainty around that point estimate). IV, inverse difference

TABLE 15 Subgroup analysis: summary from Michel 2005¹⁰⁸

Study	Subgroup	Outcome	Change from baseline/difference between groups	p-value
Michel 2005 ¹⁰⁸	Patients with minimum joint space width ≥ 1 mm at entry (I: $n = 114$, C: $n = 111$)	Minimum joint space width	Change from baseline:	0.01
			I: +0.05 mm, SD 0.53 (95% CI -0.05 to 0.14)	
			C: -0.14 mm, SD 0.57 (95% CI -0.25 to -0.03)	
		Difference: 0.19 mm, SD 0.55 (95% CI 0.04 to 0.33)		
		Mean joint space width	Change from baseline:	0.006
			I: +0.01 mm, SD 0.54 (95% CI -0.09 to 0.11)	
C: -0.20 mm, SD 0.58 (95% CI -0.31 to -0.09)				
Difference: 0.21 mm, SD 0.56 (95% CI 0.06 to 0.36)				

C, control; I, intervention.

TABLE 16 Summary of the effect of chondroitin on pain, function and composite measures of health status

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value
Michel 2005 ¹⁰⁸	WOMAC total	I: 2.3, SD 1.6 C: 2.6, SD 1.7		Change from baseline: I: -3.9% C: +2.1%	NS
		I: 2.5, SD 1.6 C: 2.7, SD 1.8		Change from baseline: I: -11.0% C: -6.2%	NS
	WOMAC function	I: 2.1, SD 1.6 C: 2.5, SD 1.8		Change from baseline: I: -7.8% C: -4.6%	NS
		I: 3.0, SD 2.3 C: 3.5, SD 2.5		Change from baseline: I: -0.8% C: +5.9%	NS
Uebelhart 1998 ¹¹⁴	Huskisson VAS (0-10 cm)	I: 5.76 cm, SD 1.61 C: 6.44 cm, SD 1.10	I: 2.1 cm, SD 2.1 C: 4.8 cm, SD 2.5		Between treatments $p < 0.001$, between times $p < 0.05$
		I: 5.1 cm, SD 1.5 C: 5.7 cm, SD 1.6	I: 8.6 cm, SD 1.4 C: 6.8 cm, SD 2.3		Between treatments $p = NS$, between times $p < 0.001$
	Overall mobility capacity (VAS)	I: 9.0, SD 2.8 C: 9.1, SD 3.2	I: 5.8, SD 3.6 C: 7.0, SD 3.9	I: -36% C: -23%	< 0.01
		I: 58.8 mm, SD 15.5 C: 61.1 mm, SD 19.0	I: 34.3 mm, SD 27.4 C: 45.8 mm, SD 27.6	I: -42% C: -25%	< 0.05
Uebelhart 2004 ¹¹⁶	Lequesne index	I: 24.5 seconds, SD 22.7 C: 22.8 seconds, SD 7.5	I: 20.1 seconds, SD 6.8 C: 22.7 seconds, SD 7.7	I: -18% C: -0.5%	< 0.05

C, control; I, intervention; NS, not significant; VAS, visual analogue scale.

for walking time [a decrease of 4.4 seconds in the intervention group and 0.1 seconds in the placebo group ($p < 0.05$)].

Function/pain composite scores Michel did not find any significant differences between chondroitin sulphate and placebo for the WOMAC total score. However, the trial by Uebelhart (2004) found a statistically significant result in favour of chondroitin sulphate for the Lequesne index [a decrease of 3.2 points in the intervention group and 2.1 points in the placebo group ($p < 0.01$)].

Adverse events None of the chondroitin trials found significant differences in reported adverse effects between the chondroitin groups and the placebo groups. No significant differences in routine laboratory test results (where reported) were seen.

Combination therapy with glucosamine and chondroitin

Trial characteristics

Both trials of glucosamine and chondroitin combination therapy were double-blind, placebo-controlled single centre trials with a duration of 1 year. The trial by Messier¹²² was industry funded; no funding information was available for Rai.¹²⁰ A total of 189 people participated in these trials. The mean age was between 70 and 74 years for Messier and around 54 years for Rai. The trial by Messier included more women than men (between 66% and 76% women); no gender information was given by Rai. Neither of the trials gave details of OA severity or duration. Rai reported baseline characteristics to be well balanced in the comparison groups, whereas in the trial by Messier, participants in the intervention group were significantly younger, more overweight, and had a higher income than those in the placebo group.

Interventions

In the trial by Rai, it was only stated that Kondro, an oral combination of glucosamine sulphate and chondroitin sulphate, was given. No details on dosing were given, but the Kondro capsules contain 250 mg glucosamine sulphate and 200 mg chondroitin sulphate, and presumably one capsule a day was given. In the trial by Messier, a combination of 1500 mg glucosamine hydrochloride plus 1200 mg chondroitin sulphate was given each day, either in one dose or distributed over three doses a day. During the first 6 months, this was supplemented in both comparison groups by six healthy lifestyle classes, and in the second 6 months, an exercise programme was added that lasted for 6 months.

The exercise programme was home and facility based and consisted of two 15-minute walking sessions, separated by 20 minutes of strength training. Exercise sessions were held for an hour each twice a week. In the trial by Messier, paracetamol was allowed as a rescue medication. In the trial by Rai, patients were advised to take paracetamol for pain. Messier did not report whether the difference in analgesic consumption between the groups was significant (a decrease of 37% by 12 months in the intervention and 11% in the placebo group), and Rai did not report analgesic consumption.

Outcome measures and further trial details are summarised in *Table 10*.

Trial quality

The trial by Messier was of moderate quality, whereas the trial by Rai was of poor quality. Messier did not explicitly describe randomisation, but their description implies that randomisation was done centrally by the sponsor. Rai did not report the method of randomisation, it was unclear whether allocation was concealed and the study was described as double blind, but no further detail was given, withdrawals or drop-outs were not reported, and it was not reported whether analysis was by intention to treat.

Results

Structure Rai found a statistically significant result for the preservation of minimum joint space with a combination of glucosamine sulphate and chondroitin sulphate compared with placebo [change from baseline -0.04 mm in the intervention group and -0.13 mm in the placebo group ($p \leq 0.01$)]. *Table 17* summarises the trial findings for the effects on structure.

Symptoms/pain *Table 18* summarises the findings for symptoms and pain.

Pain Messier did not report any statistically significant difference in the pain component of WOMAC at 6 or 12 months. Rescue analgesia use was decreased in both the treatment and placebo groups, but there was no statistically significant difference between the groups. Rai did not report on pain as a separate score nor did they report on analgesia use.

Function Messier did not find any statistically significant differences either at 6 months (i.e. before the exercise intervention) or at 12 months for a combination of glucosamine hydrochloride

TABLE 17 Summary of the effect of combined glucosamine and chondroitin versus placebo on structure

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	p-value
Rai 2004 ¹²⁰	Minimum joint space width	I: 3.66 mm C: 3.65 mm	I: 3.62 mm, $p = \text{NS}$ vs baseline C: 3.52 mm, $p \leq 0.01$ vs baseline		≤ 0.01

C, control; I, intervention; NS, not significant.

plus chondroitin sulphate plus exercise (versus placebo plus exercise) for any of the following outcomes: WOMAC function subscale, the distance walked in 6 minutes or knee concentric extension strength. The intervention group had a statistically significant benefit for knee concentric flexion strength and balance.

Pain/function composite scores Messier did not find any statistically significant differences either at 6 months or at 12 months for a combination of glucosamine hydrochloride plus chondroitin sulphate plus exercise versus placebo plus exercise for results of the WOMAC total score. In the trial by Rai, a statistically significant benefit of the combination treatment compared with placebo was seen on the Lequesne index. However, compared with other studies reporting results of the Lequesne index, the deterioration seen in this trial in the placebo group seems rather extreme (4.6. to 3.7 in the intervention group versus 4.9 to 11.48 in the placebo group).

Adverse events Neither of the trials of glucosamine/chondroitin combination therapy reported systematically on adverse effects.

Adverse effects of glucosamine or chondroitin – additional data

No long-term observational studies were identified that investigated any adverse events association with glucosamine (any form) or chondroitin sulphate or a combination of the two.

Anderson and colleagues⁶⁴ conducted a review of adverse effects of glucosamine which did not have the characteristics of a systematic review, but seemed to aim at some thoroughness (literature search described, obviously some formal extraction of data). For their safety assessments in humans, they summarised data from 33 studies in 3063 patients. In 16 studies of a total of 854 participants followed for a weighted average of 37 weeks, no significant changes in blood glucose values

were seen with glucosamine administration at therapeutic doses. In 13 studies including over 800 participants, no laboratory or cardiovascular abnormalities were seen with glucosamine administration at therapeutic doses for a weighted average of around 40 weeks. Studies reporting common adverse events included 988 participants followed for a weighted average of 37 weeks. Adverse events were reported less frequently with glucosamine than with placebo [rate ratio 0.76 (95% CI 0.61 to 0.92, $p < 0.05$)]. Five studies reported adverse events with glucosamine in comparison with adverse events with ibuprofen, and the prevalence of adverse events was 10.0% with glucosamine and 32.5% with ibuprofen.

Stumpf and colleagues¹³² reviewed data on the effect of glucosamine on glucose control. The review was not a systematic review, but a search strategy was described. Of 16 clinical studies of oral glucosamine, only five included plasma glucose concentrations that could be pooled. After 3–12 weeks of treatment, glucose values in the glucosamine groups were not significantly different from those in the placebo groups. Two 3-year studies (Pavelká and colleagues⁷⁷ and Reginster and colleagues⁷⁶) also found no significant effect on glucose levels. However, the authors concluded that data were limited and longer-term effects were uncertain.

One RCT by Scroggie and colleagues¹³³ studied 34 patients with type 2 diabetes and a mean age of 69–71 years. Patients in the intervention group ($n = 22$) were given a combination of 1500 mg glucosamine hydrochloride plus 1200 mg chondroitin sulphate per day. Twelve patients were in the placebo group. After 90 days of treatment, glycaemic control (HbA1c levels) were not significantly different between the comparison groups.

Knudsen and Sokol¹³⁴ presented a case report of a potential interaction of glucosamine/chondroitin with warfarin in a single patient, resulting in an

TABLE 18 Summary of the effect of combined glucosamine and chondroitin versus placebo on measures of pain, function and composite health status scores

Study	Outcome	Baseline	End of study	p-value
Messier 2007 ¹²²	WOMAC pain	I: 7.1, SE 0.5 C: 5.9, SE 0.5	6 months: I: 6.2, SE0.4 C: 6.2, SE0.4 12 months: I: 6.0, SE0.5 C: 5.18, SE0.5	NS
	WOMAC function	I: 25.9, SE 1.7 C: 21.1, SE 1.5	6 months: I: 21.9, SE 1.1 C: 22.9, SE 1.1 12 months: I: 19.4, SE 1.2 C: 20.6, SE 1.2	NS
	6-minute walk	I: 384.7m, SE17.6 C: 398.7m, SE17.3	6 months: I: 393.6m, SE 8.0 C: 396.5m, SE 7.9 12 months: I: 409.2m, SE 8.7 C: 410.5m, SE 8.6	NS
	Knee concentric extension strength	I: 209.4 N, SE 31.2 C: 163.9 N, SE 20.6	6 months: I: 176.9 N, SE 16.3 C: 202.7 N, SE 17.5 12 months: I: 207.6 N, SE 14.6 C: 209.7 N, SE 15.0	NS
	Knee concentric flexion strength	I: 106.0 N, SE 16.1 C: 83.0 N, SE 10.9	6 months: I: 106.1 N, SE 7.3 C: 106.7 N, SE 7.8 12 months: I: 102.9 N, SE 7.7 C: 124.8 N, SE 8.3	NS at 6 months, p = 0.05 at 12 months
	Balance (foot length)	I: 0.52, SE 0.04 C: 0.53, SE 0.03	6 months: I: 0.523, SE 0.014 C: 0.583, SE 0.017 12 months: I: 0.538, SE 0.017 C: 0.591, SE 0.020	p = 0.01 at 6 months, p = 0.05 at 12 months
	Rai 2004 ¹²⁰	Lequesne index	I: 4.6 C: 4.9	I: 3.7 C: 11.48

C, control; I, intervention; N, Newton; NS, not significant.

increased international normalised ratio (INR) (i.e. a higher risk of bleeding). The authors did a search of the US FDA MedWatch database and the WHO Adverse Drug Reactions database, as well as a literature search of MEDLINE, EMBASE

and the International Pharmaceutical Abstracts database. They identified 43 unique cases of an increased INR in people using warfarin and glucosamine or a glucosamine/chondroitin sulphate combination product (20 cases from MedWatch, 21

cases from the WHO database, and one published case report). The reports showed a temporal relationship between glucosamine or combination product use and warfarin, with a number of the reports stating that patients had a stable INR when they started taking glucosamine, and that the event resolved again in most cases when glucosamine was stopped. The Therapeutic Goods Administration of the Australian Government has received 12 reports (nine included in the WHO data) of interactions between warfarin and glucosamine. In 10 of these case reports, clinically significant rises in INR were observed 4–20 days after initiation of glucosamine.¹³⁵

A case report in the UK¹³⁶ reported the death of a man who developed acute liver failure. The otherwise healthy 64-year-old man had recently started treatment with glucosamine. A fatal accident enquiry concluded that there was insufficient evidence to attribute the death to glucosamine.

Summary

We summarise below the evidence of clinical effectiveness of glucosamine and chondroitin, highlighting where data were suitable for inclusion in economic modelling and where there were important gaps or uncertainty in the evidence.

Systematic reviews

This review summarised five systematic reviews and one clinical guideline – two on glucosamine, two on chondroitin and two on glucosamine and/or chondroitin for OA of the knee. Taken together, the reviews summarised 45 trials – 21 of glucosamine, 20 of chondroitin sulphate and four of a combination of glucosamine and chondroitin. There were considerable differences between the reviews in terms of the studies included – with respect to parameters such as study duration, comparison interventions and inclusion of treatment for disorders other than OA of the knee. In particular, the lack of presentation of analysis for all outcomes and conclusions separately for long-term studies made it difficult to draw conclusions about the effectiveness of glucosamine and chondroitin on long-term OA disease progression. This was less of an issue for structural change outcomes as few studies presented this finding, and where they did, the duration was generally longer. No major safety concerns were highlighted in the reviews. We, therefore, focused our assessment of clinical effectiveness on analysis of primary RCTs

and we included eight trials that met our inclusion criteria of at least 12 months' follow-up.

Evidence of clinical effectiveness

Glucosamine

Two RCTs^{76,77} investigated glucosamine sulphate, both using the Rotta preparation (including a total of 414 participants), and one¹²³ investigated glucosamine hydrochloride (including a total of 142 participants). Owing to the small number of trials eligible, we could not compare different forms of glucosamine preparations, different doses or monotherapy with combination therapy.

Glucosamine sulphate (Rotta product)

Our meta-analysis showed a statistically significant effect of glucosamine sulphate in comparison with placebo on joint space width. The clinical significance, while not meeting the pre-stated meaningful change used by trialists when calculating study power (change of 0.33–0.50 mm reported), was supported by the 8-year follow-up data that showed significantly fewer knee arthroplasties in the glucosamine group than in the placebo group (6.3% versus 14.5%; RR 0.43). Both trials also found statistically significant results in favour of glucosamine for almost all pain and function parameters examined (except WOMAC stiffness in one trial). The clinical significance was uncertain. No a priori clinically significant change was specified by the trialists. Changes in function were less than suggested by Tubach and colleagues³⁹ to be of clinical importance. It is important to note that both these trials used the Rotta preparation, a powdered oral form of glucosamine.

Participants in the two relevant trials were slightly younger than might be expected in a clinical population of people with OA of the knee (mean 61–66 years) and included a high proportion of women (75–79%). Participants had experienced OA for variable durations with a mean of 8–10 years, but with substantial heterogeneity. One of the trials⁷⁷ required participants to have a Lequesne index of at least 4 and not exceeding 12, and so excluded people with mild symptoms (1–4) and those with very severe symptoms. The recruited population had a mean score of approximately 9 at baseline reflecting 'severe' symptoms. Obese people were excluded from the trials. As indicated in Chapter 2, the decision to undertake knee arthroplasty is based on clinical assessment but is influenced by many factors, including patient and health service characteristics. The comorbidities of participants were poorly reported. The clinical

setting for the two trials in the Czech Republic and Belgium may differ substantially from the UK. In the UK, there are few data about the proportion of people with OA receiving knee arthroplasty, so it is difficult to determine if the surgical rate of 14.5% in 8 years from 'referral' (plus a mean of 8 years of OA prior to referral) reflects practice that is generalisable to the UK.

In addition, the studies with 8-year follow-up ended as RCTs after 3 years. During the ensuing follow-up, participants were not restricted to treatment choices and substantial treatment group switching may have occurred. The study design, utilising routine health-care data to identify knee arthroplasties, precluded the gathering of information about medicine use after the RCT ended or further information about QoL. This switching would, if anything, lessen the effect size observed when comparing the treatment and control groups based on their original trial allocation.

Glucosamine hydrochloride

Only one poor quality trial of glucosamine hydrochloride was identified.¹²³ No significant differences between glucosamine hydrochloride and the placebo control were seen for any of the structural, pain or functional outcomes assessed. We therefore have very limited evidence about the effectiveness of hydrochloride preparations, and nothing to support its clinical effectiveness.

Chondroitin

Three studies investigated chondroitin sulphate (including a total of 456 participants).^{108,114,116} Our meta-analysis showed small, but statistically significant effects on both mean and minimum joint space width in favour of chondroitin sulphate. As noted previously, while this surrogate end point has been widely used within trials, the clinical significance of joint space narrowing in relation to long-term disease progression and knee arthroplasty is uncertain. The lack of correlation between symptoms and joint space loss makes it difficult to translate this outcome into a measure of health utility that can be utilised in any health economics modelling. There were no studies following participants for sufficient duration to assess the effect on knee arthroplasty. Results for pain and function were not consistent between studies, with studies using different tools to measure effect. Of the two larger, good quality studies, one¹⁰⁸ reported no significant effect on WOMAC scores while the other¹¹⁶ found improvements on the Lequesne index for both the placebo (2 points) and treated (3 points)

groups. While statistically significant, the clinical significance of a 1-point difference on this scale is uncertain. The Lequesne index is scored out of 24, but anything over 13 is considered to represent extremely severe symptoms.

Combined glucosamine and chondroitin

Two poor-to-moderate quality studies investigated a combination of glucosamine (one of glucosamine sulphate, one of glucosamine hydrochloride) and chondroitin (including a total of 189 participants).^{120,122} Only one of the trials¹²⁰ measured joint space parameters and found a statistically significant result in favour of the treatment with respect to loss of minimum joint space width. One trial¹²² did not report any significant difference between the combination therapy and placebo on any of the WOMAC parameters measured. The other trial¹²⁰ reported a clinically and statistically significant effect on the Lequesne index, with an improvement in the treated group and a worsening of the mean score from moderate to very severe. However, the study was of poor quality with unclear randomisation, allocation concealment and analysis.

The observational GAIT ancillary study was not included in this review, but reported differences in joint space loss that were not statistically significant when comparing glucosamine, chondroitin or a combination of glucosamine and chondroitin with placebo. The smallest joint space loss was observed in the glucosamine group, but the study suffered from being underpowered, with fewer participants meeting the inclusion criteria than anticipated.

All of the reviews or trials examined suggested that there were no safety concerns with glucosamine or chondroitin sulphate. Examination of additional literature suggested that glucosamine (and probably chondroitin) does not have any significant effect on glucose homeostasis, despite clinical concerns that there may be an impact, or on the incidence of any other adverse events or laboratory abnormalities. However, a possible interaction in people taking warfarin was suggested. In general, the studies investigating relevant adverse events parameters were small and data on long-term follow-up were lacking. The association with acute liver toxicity is uncertain.

Table 19 gives a summary of the findings from the clinical effectiveness review focusing on effect after at least 12 months' follow-up. Statistical significance is reported, but may not necessarily reflect clinically important differences.

In conclusion, we found evidence of long-term effectiveness for the Rotta product of glucosamine sulphate from two good quality trials, although both were funded by the manufacturers. The evidence of modification to structural change was supported by a difference in rate of knee arthroplasty after 8 years of follow-up. WOMAC scores were measured for 3 years and demonstrated minor improvements, of borderline clinical

importance, in both the treatment and control groups. There was evidence of no reduction in the use of analgesia and very limited long-term safety data but no safety issues were identified in short-term studies. For all other preparations, there was insufficient evidence of effectiveness, heterogeneity in the trial data or no evidence to enable conclusions to be drawn.

TABLE 19 Summary of findings from the clinical effectiveness review

Effect	Evidence summary
Glucosamine sulphate prevents or slows progression (compared with placebo):	
Joint space loss	Evidence of effectiveness
Pain/function	Evidence of effectiveness
Knee arthroplasty	Evidence of effectiveness
Reduction in need for analgesia	Evidence of no effectiveness
Glucosamine hydrochloride prevents or slows progression (compared with placebo):	
Joint space loss	Evidence of no effectiveness (poor quality)
Pain/function	Evidence of no effectiveness (poor quality)
Knee arthroplasty	No evidence
Reduction in need for analgesia	Evidence of no effectiveness (poor quality)
Chondroitin prevents or slows progression (compared with placebo):	
Joint space loss	Evidence of effectiveness
Pain/function	Heterogeneity of results
Knee arthroplasty	No evidence
Reduction in need for analgesia	Mixed evidence
Glucosamine/chondroitin combination prevents or slows progression (compared with placebo):	
Joint space loss	Evidence of no effectiveness (poor/moderate quality)
Pain/function	Heterogeneity of results
Knee arthroplasty	No evidence
Reduction in need for analgesia	Evidence of effectiveness (poor/moderate quality)
Combination offers greater gains over single medicine treatment	No evidence
Identification of optimal dose or product	No evidence
Assurance of safety	
Short-term/trial setting	Evidence of safety
Long-term/clinical setting	Very limited evidence

Chapter 4

Cost-effectiveness of glucosamine and chondroitin in OA of the knee

Introduction

The review of clinical effectiveness shows that of the therapies that were reviewed, only glucosamine sulphate was demonstrated to have a statistically significant effect on QoL and/or disease progression. Thus, cost-effectiveness modelling was limited to a comparison of glucosamine sulphate versus current care. The model draws upon several data sources, including the paper by Bruyere and colleagues,⁵² which uses pooled data from two previous RCTs of the clinical effectiveness of glucosamine sulphate.^{76,77} However, there was a lack of data on costs and QoL from the pooled study. Thus, the model also draws upon other studies that report this information. Further detail is outlined in the Methods section and Appendix 7. One important issue to note relates to the definition of current care. In the model presented below, estimates of the costs of current care are based on two UK sources,^{32,137} while estimates of comparative effectiveness are based on the definition of current care used by Bruyere and colleagues,⁵² that is: ‘...any care received from health-care providers, with or without physical therapies and investigations (hydrotherapy, exercise, ultrasound, radiological procedures), and treatment with

prescribed medicines (includes antacids, hypnotics and anxiolytics, antidepressants, analgesics, corticosteroids, drugs for nutritional, blood, musculo-skeletal and joint diseases, and local anaesthetics)’.

Methods

The costs and effectiveness of glucosamine sulphate were modelled using cohort simulation (*Figure 8*). Cohort simulation involves the placement of a number of individuals with pre-defined baseline clinical characteristics into particular states of health, with associated costs and QoL, who may then move or not move to other states of health over time. Owing to a lack of well-defined discrete states in knee OA, the approach taken here involved the placement of the cohort into an initial baseline level of health status, followed by change in health status over time. Thus, rather than using discrete states, health was modelled along a continuum. In addition to the continuous health status measure, two additional states were used. First, to reflect the greater costs and QoL implications associated with knee replacement arthroplasty, a separate state was included for this

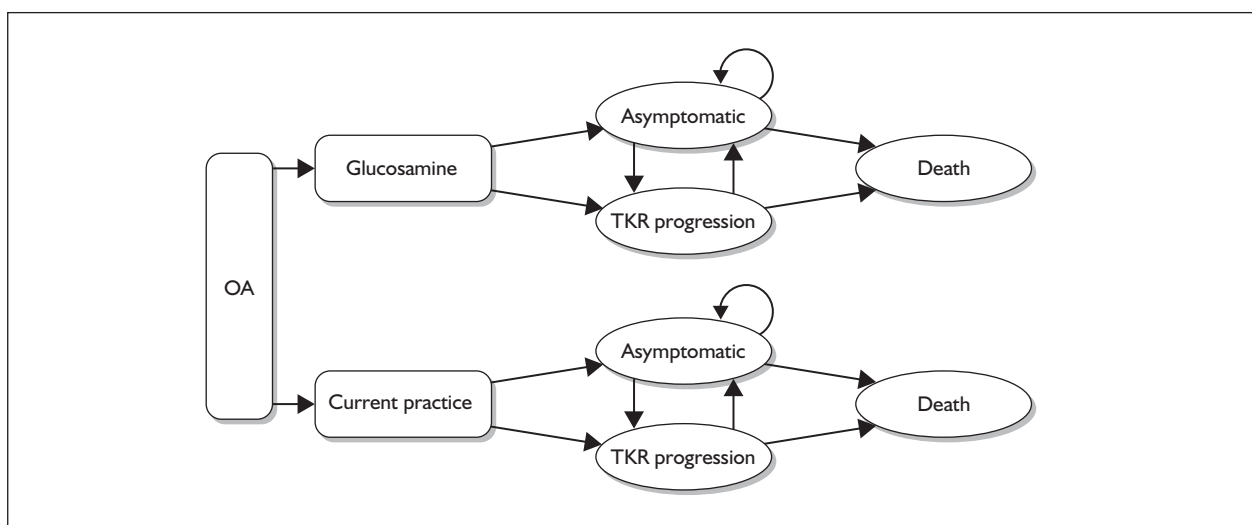


FIGURE 8 Outline schematic of model structure. TKR, total knee replacement.

outcome. Knee arthroplasty can include a number of different surgical procedures. For the purpose of the model, total knee replacement (TKR) surgery was assumed. Further, although therapy had no effect on survival, as the time horizon was remaining lifetime, the state of death was also included. An outline schematic of model structure is shown in *Figure 8*.

The cohort was pre-defined according to the baseline clinical characteristics reported within Pavelká and colleagues.⁷⁷ We used this source as this was the only published randomised placebo-controlled trial of therapy that reported baseline and follow-up QoL data, using an instrument (WOMAC) that permitted conversion to a preference-based utility scale (HUI3). The conversion from Likert WOMAC score to HUI3 was performed using Grootendorst and colleagues.¹³⁸ Grootendorst and colleagues¹³⁸ conducted a multicentre randomised trial of hylan G-F 20 against appropriate care among 255 Canadian patients with symptomatic knee OA of mild to moderate severity, who had previously been treated with analgesics, in which patients completed WOMAC and HUI3 questionnaires at 2-monthly intervals over 12 months. It is important to use preference-based scales such as the HUI3, in order to permit comparisons of cost-effectiveness with other therapies using quality-adjusted life-year (QALY) measures. A recent paper,¹³⁹ published after model development, has produced EQ-5D estimates derived from WOMAC for knee pain patients. However, as the model does not account for disease duration, and was not derived from a population of knee OA patients, we chose to retain the Grootendorst and colleagues' mapping algorithm.¹³⁸

Based on Pavelká and colleagues⁷⁷ and Grootendorst and colleagues,¹³⁸ the cohort had an initial QoL score of 0.69 (on a 0–1 scale, where 0 = dead and 1 = perfect health). It is useful to note that this value is identical to the EQ-5D based value from Barton and colleagues,¹³⁹ used by the NCCCC,¹ which modelled the cost-effectiveness of oral NSAID or COX inhibitor therapy for OA. The value of 0.69 was computed using the best performing model (model 3); this model had the lowest mean absolute error (MAE) and the lowest root mean square error statistics (RMSE) (MAE = 0.1628, RMSE = 0.2065), relative to the closest alternative model that included Kellgren radiographic grade (MAE = 0.1638, RMSE = 0.2083). Model 3 is shown as follows:

$$\begin{aligned} \text{Predicted HUI3 utility score} = & 0.5274776 + \\ & (0.0079676 \times \text{pain}) + (0.0065111 \times \text{stiffness}) \\ & - (0.0059571 \times \text{function}) + (0.0019928 \times \text{pain} \\ & \times \text{stiffness}) + (0.0010734 \times \text{pain} \times \text{function}) + \\ & (0.0001018 \times \text{stiffness} \times \text{function}) - (0.0030813 \\ & \text{pain}^2) - (0.0016583 \times \text{stiffness}^2) - (0.000243 \\ & \times \text{function}^2) + (0.0113565 \times \text{age in years}) - \\ & (0.0000961 \times \text{age in years}^2) - (0.0172294 \times \\ & \text{female}) - (0.0057865 \times \text{years since onset of OA} \\ & \text{in the study knee}) + (0.0001609 \times \text{years since} \\ & \text{onset of OA in the study knee}^2). \end{aligned}$$

The authors show with the aid of a worked example that the model predicts that a 56-year-old woman with WOMAC pain, stiffness, and function scores of 10, 5, and 24, respectively, who has had OA for 2.5 years, would have a HUI3 score of 0.68. For our cohort, we obtained a similar value (0.69) to this with different parameters. We used less disabled WOMAC pain, stiffness and function scores of 6, 2 and 22 (the higher the score, the worse the disability), and higher values for OA duration and age, reported from the mean intention-to-treat values in the placebo group in Pavelká and colleagues.⁷⁷ We were only able to use the Pavelká and colleagues⁷⁷ estimate as Reginster and colleagues⁷⁶ reported VAS WOMAC scores rather than the Likert version. Further, for ease of illustration we approximated the Pavelká and colleagues⁷⁷ demographic estimates by using OA duration of 10 years and a starting age of 60 years (the mean values in the placebo group were 11 years and 63 years respectively).

Once the cohort was placed in the starting level of health, thereafter individuals had a particular probability of entering the TKR state, or avoiding TKR and progressing to a different state of health, or dying. Within the glucosamine group, individuals were assumed to remain on therapy until death. Probability of entering the state of TKR was derived from Bruyere and colleagues;⁵² the TKR risk was annualised using a standard formula, $p^* = 1 - (1 - p)^{1/t}$, where p = event probability over study duration and t = time in years. Probability of death was estimated from age-specific all-cause life tables.¹⁴⁰ As explained above, the QoL associated with health change over time among those neither dying nor entering the TKR state was taken from Grootendorst and colleagues,¹³⁸ who estimated regression models that permit conversion of HUI3 scores using WOMAC subscale scores, age, and duration of OA in the study knee. Owing to a lack of data reporting QoL prior to TKR within Bruyere and colleagues,⁵² QoL prior to TKR was estimated

from another source, using baseline (48 hours prior to surgery) WOMAC subscale scores published by Nunez and colleagues,¹⁴¹ giving a value of 0.51. Within the model, individuals who entered the 'prior to TKR' health state did so at the beginning of each annual cycle and remained in that state for the complete cycle length, i.e. 12 months, then rejoined the larger non-progressive cohort in future cycles. Added to this, for both progressors and non-progressors, account was taken of the natural history of knee OA, using data from Johnson and colleagues,²² who reported 7-year WOMAC subscale score data for 43 Canadian patients (mean age at baseline 69 years, 77% female) with moderate to severe hip or knee OA. Converting to HUI3 using the Grootendorst and colleagues model,¹³⁸ the difference in QoL after 7 years of 0.04 gives an annual QoL decrement value of 0.006.

The effectiveness of therapy on health states was obtained from two main sources. First, we used the estimate from Bruyere and colleagues⁵² of the effectiveness of therapy in reducing the risk of undergoing TKR surgery (RR = 0.43, 95% CI 0.20 to 0.92). The Bruyere estimate was based on pooled data from 275 patients who had participated in two previous randomised placebo-controlled trials of glucosamine sulphate,^{76,77} with follow-up data for a mean period of 5 years after the end of both 3-year trial periods.

Second, the effectiveness of therapy in improving QoL for those who did not progress to TKR was estimated using Pavelká and colleagues,⁷⁷ who demonstrated a statistically significant change in WOMAC total scale and subscale scores. To generate the annual utility improvement with therapy, the WOMAC subscales scores at baseline

and follow-up, with and without therapy, were converted to HUI3 using the regression model of Grootendorst and colleagues.¹³⁸ The calculation is shown in *Table 20*.

Health-care costs associated with knee OA were estimated from a UK study conducted by Lord and colleagues.³² This study was an RCT of primary care-based education for knee OA. In both control and intervention groups, costs were related to the resources consumed for GP visits, medications, outpatient visits, inpatient care, professions allied to medicine consultations, complementary therapists and X-ray procedures for a population of patients with radiographic evidence of knee OA. Data were collected from case notes, supplemented by patient interview for data on professions allied to medicine consultations. We used the reported NHS direct cost element, uprated to 2007–8 prices, for the control group who did not receive the education programme (£216 per patient per year). This estimate was very similar to the values reported in a more recent study by Hurley and colleagues,¹³⁷ who calculated 6-month health-care and social care costs of £103 for usual care among chronic knee pain patients in the UK at 2003–4 prices. The cost of TKR surgery (£6126) was calculated by uprating to 2007–8 prices the 2005–6 NHS Reference Costs estimate for elective primary knee replacement (code HRG H04, £5747).¹⁴² We used the lower and upper interquartile range estimates, uprated to 2007–8 prices, in probabilistic analysis, applying a uniform distribution. No UK published prices were available for glucosamine sulphate, as the product has no UK licence. UK prices were, however, available for the licensed hydrochloride preparation. Listed prices for glucosamine sulphate in the USA were US\$34.95

TABLE 20 Calculation of Health Utilities Index (HUI) from WOMAC scores

	WOMAC		HUI				
	Baseline	Follow-up	Baseline	Follow-up	Difference	Annualised difference ^a	QoL gain
Placebo	Pain 6.33 Function 22.00 Stiffness 2.15	Pain 5.23 Function 18.30 Stiffness 2.26	0.687186	0.717122	0.029936	0.010080	
Therapy	Pain 6.61 Function 21.84 Stiffness 2.25	Pain 4.61 Function 16.04 Stiffness 1.94	0.689013	0.733497	0.044484	0.015050	0.004970

a Calculated using a standard formula of $1 - (1 - v)^{1/t}$, where v = HUI difference (column 6) and t = 3.

for 30 days' supply,¹⁴³ giving a total annual cost of US\$429.40 with international shipping, or £242.60 at an exchange rate of £1 = US\$1.77. Purchasing power parity (PPP) conversion from US\$ gives a cost of £280.40. The price to the NHS is likely to be cheaper, however, given that the NHS is a monopoly buyer, and glucosamine sulphate would be likely to be priced at a similar level to competitor products, such as the hydrochloride formulation. For the purposes of assessing the cost-effectiveness of a likely guide price in the future, we therefore used current UK published market prices of glucosamine hydrochloride, giving an annual cost of £221 per patient per year. In addition however, based on the PPP conversion price of £280.40, we used upper and lower bounds of 27% in deterministic sensitivity analysis to assess the impact of alternative prices on cost-effectiveness. Both costs and health outcomes were discounted at 3.5%. Assumptions for model parameters are outlined in *Table 21*.

Data analytic procedures

The sensitivity of the results to different model assumptions was explored in two ways. First, both stochastic and non-stochastic parameters were varied individually using deterministic one-way sensitivity analysis. These parameters included glucosamine sulphate acquisition costs, discount rate, proportion of patients requiring TKR surgery, health-care costs, QoL scores and TKR probabilities. *Table 22* provides information on the assumptions used to generate the lower and upper bounds for each parameter.

Second, to take account of parameter uncertainty, probabilistic sensitivity analysis was employed. This involved taking 5000 random draws from specific distributions of all stochastic parameters (current care TKR probabilities, relative risk reduction of TKR associated with therapy, current care QoL score, QoL gain with therapy, current care health-care costs, TKR costs). More details on the specific distributions used are outlined in the footnotes to *Table 23*. The distributions selected for each parameter reflect common candidate distributions.¹⁴⁶

Value of information analysis was conducted to investigate the worth of commissioning further research on the cost-effectiveness of therapy. Population expected value of perfect information (EVPI) was computed, assuming a constant population size of 500,000 knee OA patients over a discounted 10-year time horizon. To assess which parameter, or set of parameters, should be the focus for any future research, analysis of covariance techniques were used to explore the proportionate contribution of each parameter to variation in incremental cost and QALYs. This was implemented using the 'Covariance' command in EXCEL; this allows determination of whether large values of one variable tend to be associated with large values of another (positive covariance), whether small values of one variable tend to be associated with large values of another (negative covariance), or whether values of both variables tend to be unrelated (covariance near zero). We used the covariance between log incremental costs, log TKR costs, log health-care costs and

TABLE 21 Model assumptions and parameter

Parameter	Value	Data source
QoL at baseline – current care	0.687186	Pavelká 2002, ⁷⁷ Grootendorst 2007 ¹³⁸
Annual probability of progression to TKR – current care	0.019397	Bruyere 2008 ⁵²
Annual probability of progression to TKR – glucosamine sulphate	0.008035	Bruyere 2008 ⁵²
Annual probability of not progressing to TKR – current care	0.980603	Bruyere 2008 ⁵²
Annual probability of not progressing to TKR – glucosamine sulphate	0.991965	Bruyere 2008 ⁵²
QoL prior to TKR	0.511682	Nunez 2007, ¹⁴¹ Grootendorst 2007 ¹³⁸
Annual reduction in QoL due to natural history	0.005986	Johnson 2007 ²²
Annual QoL change due to glucosamine sulphate	0.004970	Pavelká 2002 ⁷⁷
Health-care costs of knee OA per patient per year	£216	Lord 1999 ³²
Health-care TKR costs	£6126	Department of Health 2006 ¹⁴²
Glucosamine sulphate acquisition costs per patient per year	£221	British National Formulary 2008 ¹⁴⁴
Discount rate	3.5%	The Green Book 2007 ¹⁴⁵

QoL, quality of life; TKR, total knee replacement.

TABLE 22 Deterministic sensitivity analysis – parameter values and assumptions

Parameter	Value	Data source and notes
Annual probability of TKR – current care	0.009698–0.029095	Bruyere 2008 ⁵² and authors' judgement. A 50% decrease and increase in probability of TKR described in Bruyere 2008 ⁵² is applied
TKR relative risk reduction	0.20–0.92	Bruyere 2008. ⁵² Range is reported 95% CIs of TKR relative risk reduction
Annual QoL change due to glucosamine sulphate	0.001242–0.008871	Pavelká 2002. ⁷⁷ Range is based on lower and upper 95% CIs of total WOMAC change score (0.77 to 5.5), expressed as percentage changes from mean difference, and applied to mean QoL change of 0.004970 calculated from Pavelká 2002 ⁷⁷
Glucosamine sulphate acquisition costs per patient per year	£161–£280	Upper value is US price of Rotta glucosamine sulphate product converted to GBP using PPP. Lower value is computed using equivalent percentage difference of 27%
Health-care costs of knee osteoarthritis per patient per year	£0–£1053	Hurley 2007. ¹³⁷ Range is lower and upper 95% CI of means costs calculated from published standard deviation of £185
Health-care TKR costs	£5171–£6938	Department of Health 2005 (Appendix NSRC1) ¹⁴⁷
Discount rate	0–5%	Authors' assumptions

QoL, quality of life; PPP, purchasing power parity; TKR, total knee replacement.

TABLE 23 Probabilistic sensitivity analysis – parameter distributions

Parameter	Data source	Distribution
Annual probability of progression to TKR – current care	Bruyere 2008 ⁵²	Beta binomial ^a (2, 98)
Relative risk of TKR with therapy	Bruyere 2008 ⁵²	Normal ^b (–0.84, 0.39)
Health-care costs of knee OA per patient per year	Lord 1999 ³² , Hurley 2007 ¹³⁷	Gamma ^c (42.14, 4.82)
TKR costs	Department of Health 2005 (Appendix NSRC1) ¹⁴⁷	Uniform ^d (5171, 6938)
QoL score – current care	Pavelká 2002, ⁷⁷ Grootendorst 2007 ¹³⁸	Beta method of moments ^e (339, 523)
QoL gain with therapy	Pavelká 2002, ⁷⁷ Grootendorst 2007 ¹³⁸	Normal (0.004970, 0.001950)
QoL prior to TKR	Nunez 2007, ¹⁴¹ Grootendorst 2007 ¹³⁸	Beta method of moments (438, 1570)

QoL, quality of life; TKR, total knee replacement.

a Beta binomial (α , β) refers to a beta distribution with α = number of events and β = sample size minus number of events.

b Uniform (α , β) refers to a uniform distribution with α = lower interquartile range and β = upper interquartile range.

c Gamma (α , β) refers to a gamma distribution with α = (sample mean/SE)² and β = SE²/sample mean.

d Normal (α , β) refers to a normal distribution with α = sample mean and β = SE.

e Beta method of moments (α , β) refers to beta distribution where α = sample mean (sample mean (1 – sample mean)/SE²) – 1 and β = sample mean * (1 – sample mean)/(SE²) – 1 – α .

TKR probability with glucosamine sulphate, and the covariance between incremental QALYs, QoL score with glucosamine sulphate, QoL prior to TKR and TKR probability with glucosamine sulphate, and then computed the proportionate contribution of each parameter to the overall sum

across parameters. In addition, we conducted EVPI for parameters, in which repeated 1000-model simulations were run with each parameter held constant in turn, while allowing other stochastic parameters to vary.

Results

Over a lifetime horizon (mean life expectancy of 22.61 years) the mean discounted costs per patient associated with current care were calculated as £4634. Care costs with the addition of glucosamine sulphate were estimated to be £7039 over the same time period. Thus, the additional discounted costs associated with glucosamine were £2405. Mean discounted QALYs were 8.17 for current care and 8.28 for glucosamine, giving a QALY gain of 0.11. Avoiding rounding error, the incremental cost per QALY gain was £21,335.

Deterministic sensitivity analysis revealed that estimates were reasonably robust to variations in assumptions (Figure 9). Estimates were most affected by changes in the QoL gain associated with therapy. Changes to the costs of current care or TKR costs had negligible effects.

The results of the probabilistic sensitivity analysis are presented in Figures 10 and 11. Figure 10 shows the scatterplot of differences in costs and QALYs from the 5000 replications. It was apparent that therapy was unlikely to be cost saving, as there were only 41 occurrences of costs within the glucosamine group being lower than those in the current care group. However, there was a wide scatter across the x-axis (depicting QALY differences).

Figure 11 shows the cost and QALY differences between therapy and current care within the cost-effectiveness acceptability curve framework. This depicts the change in the probability for differing values of willingness to pay for a QALY (or ‘ceiling ratio’). This shows that glucosamine was not expected to be cost-effective if we were only prepared to pay up to £10,000 per QALY (probability of cost-effectiveness = 0.08), but for increasing amounts of willingness to pay per QALY, the probability of cost-effectiveness rises (e.g. if we were prepared to pay up to £20,000 per QALY, the probability of cost-effectiveness = 0.43). At a willingness-to-pay ceiling ratio of above approximately £22,000, the probability of cost-effectiveness becomes greater than 0.5.

The EVPI provides an upper bound of the value of undertaking further research to reduce uncertainty over whether therapy is more cost-effective than current care. Figure 12 shows the relationship between these values and different ceiling ratios of willingness to pay per QALY. This reveals that the value of further research was high for a range of commonly applied ceiling ratios (e.g. £10,000–£50,000), and far exceeded the likely costs of research. The EVPI became lower as the ceiling ratio approached £100,000, as uncertainty surrounding cost-effectiveness became less for higher levels of willingness to pay per QALY.

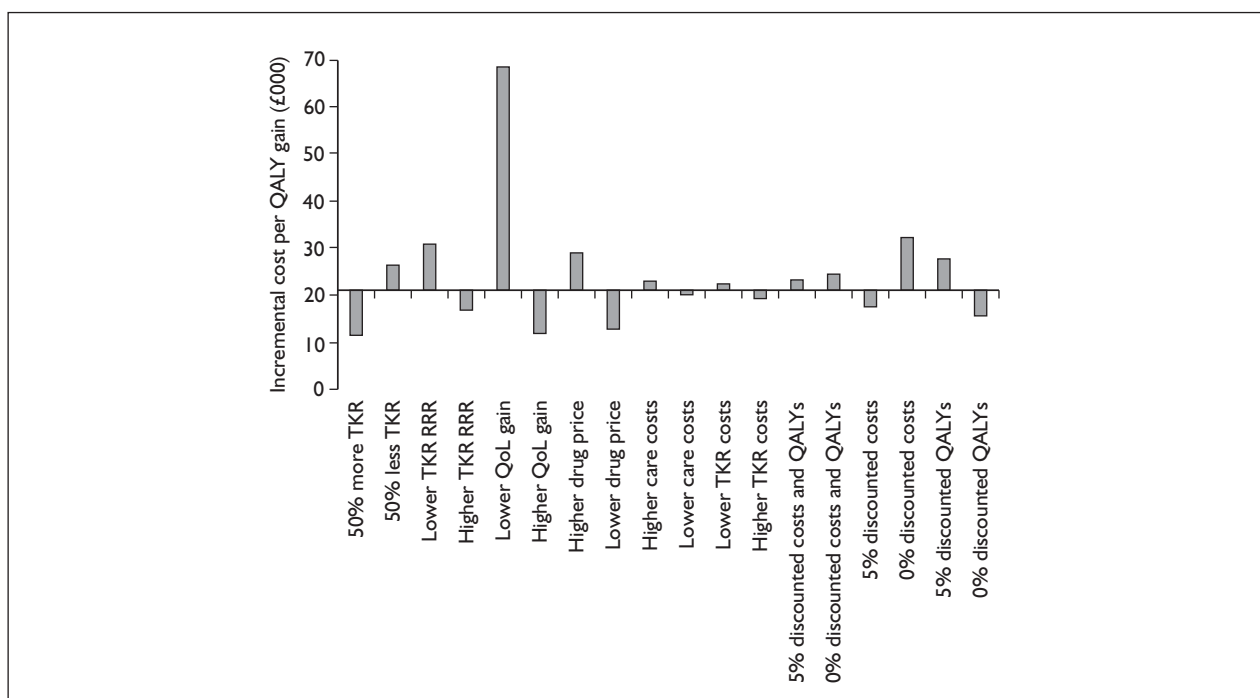


FIGURE 9 Deterministic sensitivity analysis. QALY(s), quality-adjusted life-year(s); QoL, quality of life; RRR, relative risk reduction; TKR, total knee replacement.

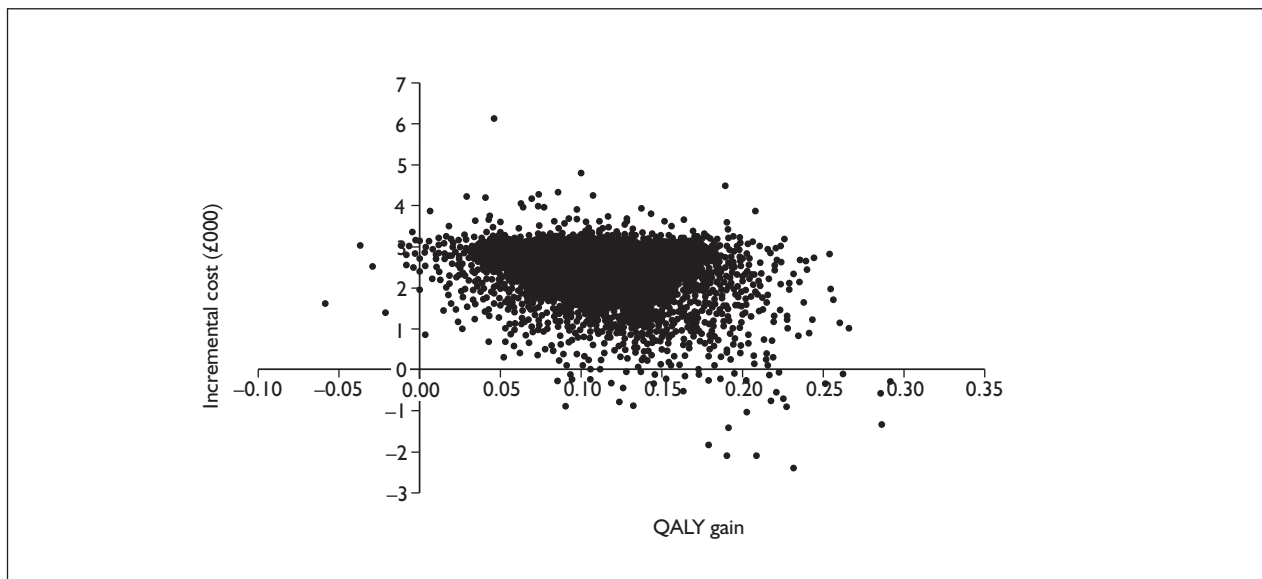


FIGURE 10 Scatterplot of incremental cost and quality-adjusted life-year (QALY) gained.

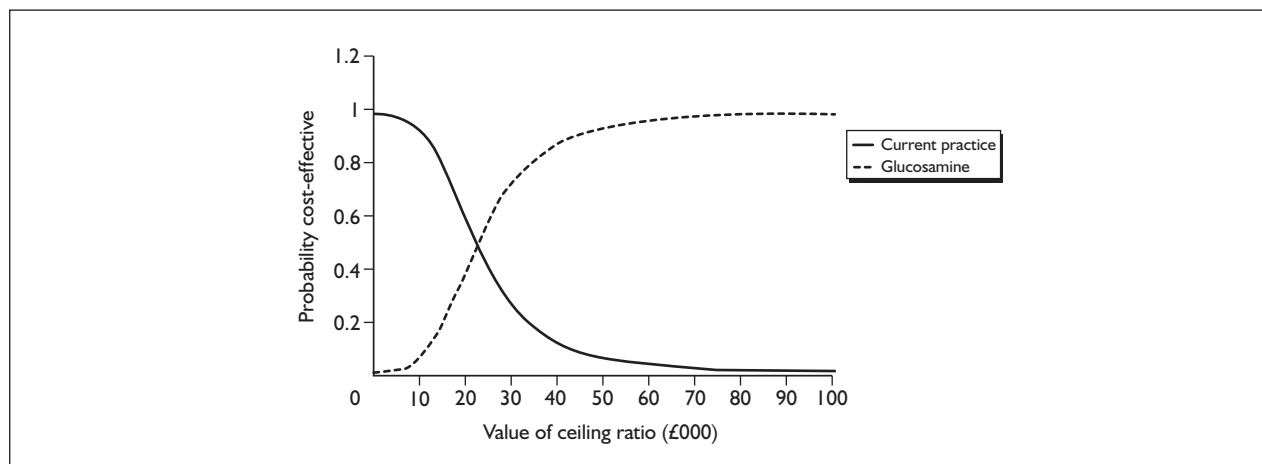


FIGURE 11 Cost-effectiveness acceptability curves.

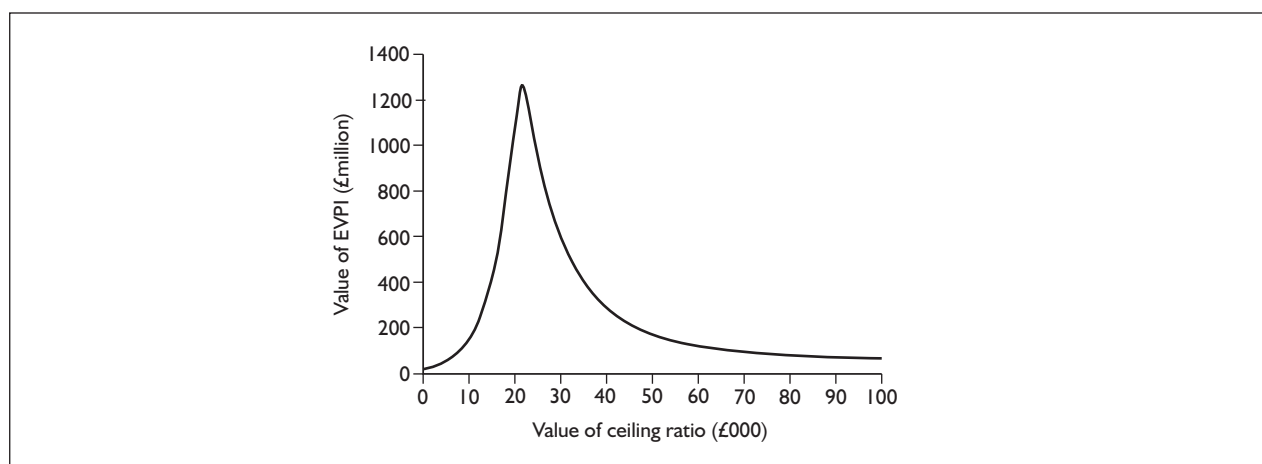


FIGURE 12 Expected value of perfect information (EVPI).

Figures 13 and 14 show the analysis of covariance results. Figure 13 reveals that the greatest uncertainty in costs was related to variation in TKR costs, followed by variation in the probability of TKR surgery with therapy, followed by variation in costs of current care. Figure 14 shows that the most important parameter that contributed to variation in QALYs was the QoL change arising from the addition of glucosamine to current care. Quality of life prior to TKR surgery, and the probability of progression to TKR surgery, make smaller, although similar, contributions in comparison. Figure 15 shows the partial EVPI for parameters. This reveals quite clearly that the most important parameter is the QoL gain associated with therapy. This is followed by the TKR probability with therapy. Current care costs, the quality of life associated with TKR and TKR costs have much smaller values in comparison.

Discussion

The addition of glucosamine sulphate therapy to current care for knee OA was estimated to lead to additional costs and gains in health-related QoL. With a cost per QALY estimate of approximately £21,335, the magnitude of potential gains appears moderate in relation to the additional costs. Deterministic sensitivity analysis suggested that the cost-effectiveness of glucosamine sulphate therapy was particularly dependent on the magnitude of the QoL gains produced by therapy. Probabilistic sensitivity analysis showed that these estimates of cost-effectiveness were imprecise, suggesting some degree of decision uncertainty.

Our estimate of cost-effectiveness was higher in comparison with other available studies; the NCCCC¹ produced two cost per QALY estimates

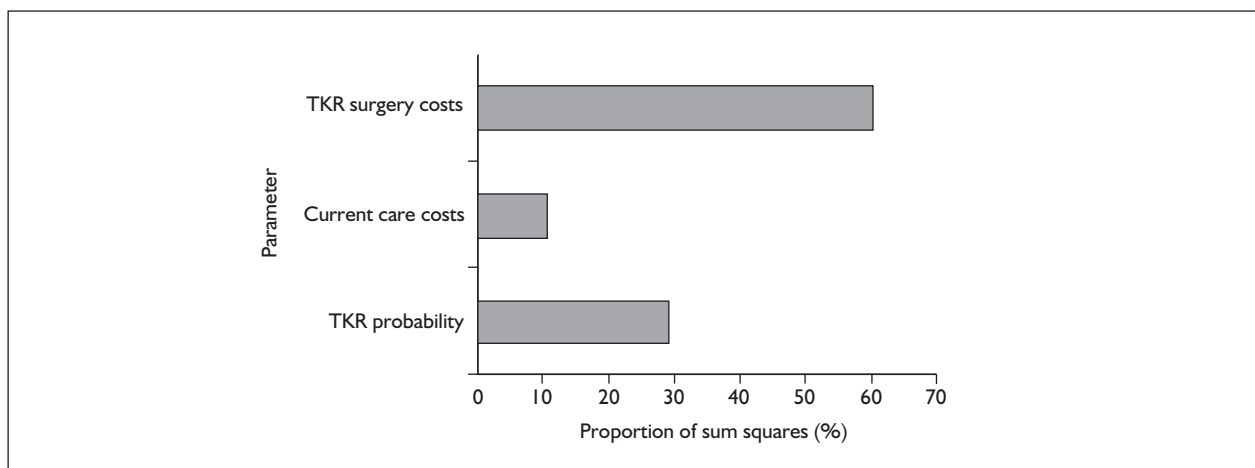


FIGURE 13 Individual parameter contribution to variation in costs. TKR, total knee replacement.

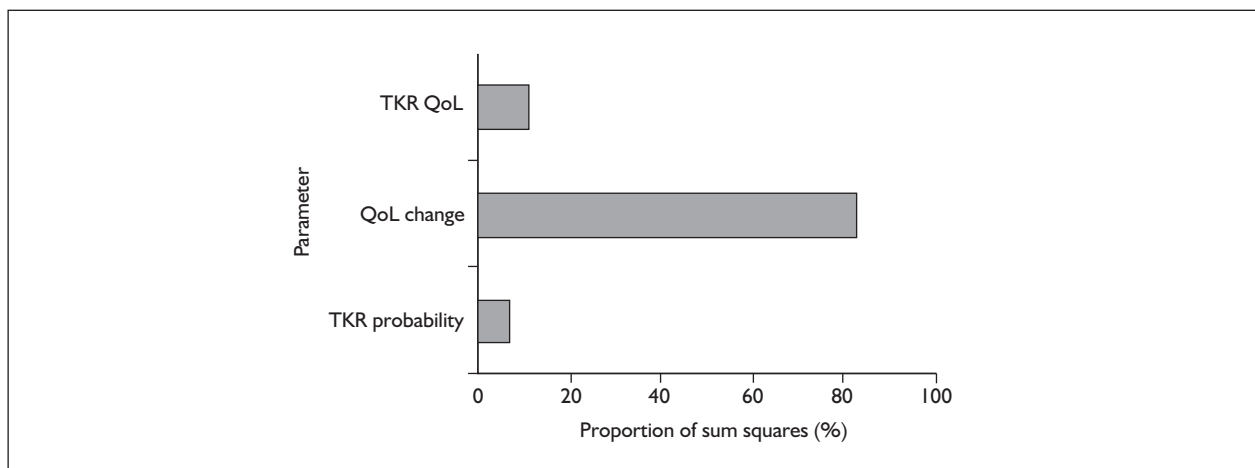


FIGURE 14 Individual parameter contribution to variation in quality-adjusted life-years. QoL, quality of life; TKR, total knee replacement.

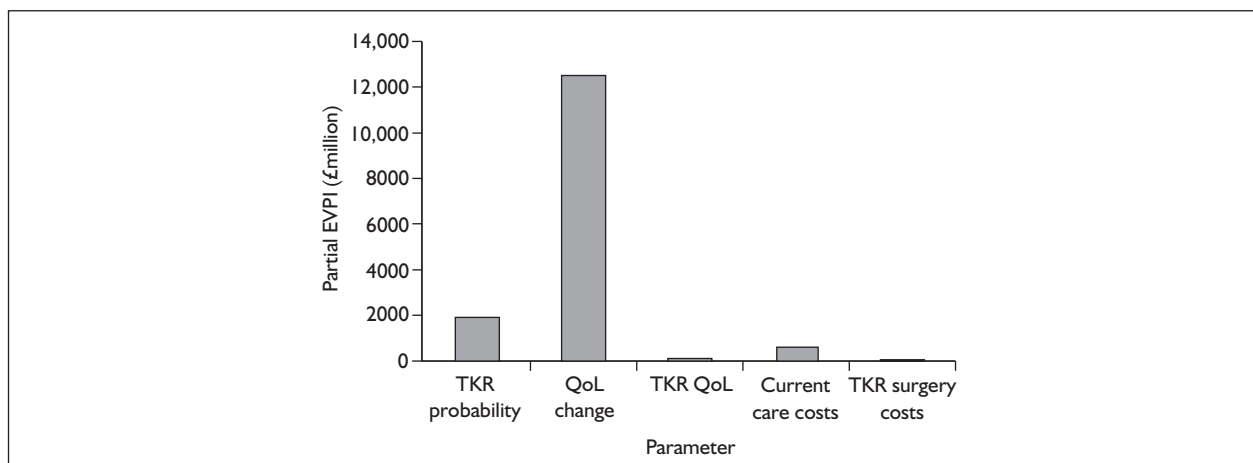


FIGURE 15 Expected value of perfect information (EVPI) for parameters. QoL, quality of life; TKR, total knee replacement.

for glucosamine sulphate. Using only 3-year data from Pavelká and colleagues,⁷⁷ the mean cost per QALY was £10,880 (range £3581–£21,219). Using data only from Reginster and colleagues,⁷⁶ the mean cost per QALY was £2427 (range £799–£6519). Without further information on the sources of data or assumptions used, it is difficult to explain the differences. One possible explanation is the difference in the timeframe adopted, although this seems unlikely, as the longer follow-up period adopted in the model presented here allows the incorporation of cost savings and QoL gains associated with the avoidance of knee replacement surgery, which would lead to lower, rather than higher, cost per QALY estimates. A more plausible explanation is the use of alternative estimates of QoL. As the same cost difference is used to generate the two estimates of cost per QALY reported by the NCCCC,¹ the cost per QALY difference is driven by differences in the QALY gain. Such differences may be due to the use of alternative ways to value health changes. For example, the lower cost per QALY gain figures of Reginster and colleagues⁷⁶ is generated from use of the VAS version of the WOMAC rather than the Likert scale version.

Value of information analysis indicated that further research to reduce decision uncertainty would be beneficial. It would appear that a high priority should be given to obtaining further evidence of the QoL gains produced by glucosamine sulphate relative to placebo. The current uncertainty surrounding the magnitude of such gains may be related to sample size and the requirement to map between health status instruments to obtain suitable QoL values in order to calculate QALYs. Thus, any future trial should aim to collect data

using a generic preference-based QoL instrument, such as the HUI3, SF-6D or EQ-5D.

It is important to emphasise that the effectiveness data within economic model are built mainly around data from one study that pooled data from two trials,⁵¹ while the QoL gain with therapy is estimated from one trial.⁵⁸ Further evidence is also required on the relationship between QoL and costs. Owing to lack of data, other than through progression to TKR surgery, it was not possible to build into the model estimates of cost changes that arise from changes in QoL. This may be an important limitation of the current model. We would anticipate that incorporation of these effects would have made current cost estimates less precise, as there was large variation around the magnitude of QoL improvements, but would have made little change to mean cost per QALY estimates. This suggests that a future trial should also collect resource use and cost data, to allow estimation of the resource impact of changes in QoL.

Estimates were not particularly sensitive to QoL prior to TKR surgery, nor to costs of surgery. Further, cost-effectiveness was moderately related to the volume of TKR surgery in deterministic analysis. To assess the importance of this parameter, we were only able to apply arbitrary 50% changes in volume in deterministic sensitivity analysis, resulting in small changes of between 1% and 2% in either direction in the likelihood of requiring surgery. A nationally representative cohort survey to determine the current level of TKR surgery would help to ensure that the modelled estimates presented here are generalisable to the UK health-care system.

Chapter 5

Biological plausibility

At the start of this review, we considered the possibility that the findings of the review of clinical effectiveness would be inconclusive – not only uncertain about whether the compounds were clinically effective, but also that there might not be sufficient basis to justify a large HTA trial. In that situation, evidence or not of biological plausibility might help to decide whether it was worth doing a trial. For example, if (as has been alleged by one commentator) none of the glucosamine taken orally reaches the bloodstream, then that would seem a good reason for not doing a trial.

The initial, rather simplistic presumption was that exogenous administration of the precursors of cartilage would in some way either aid cartilage regrowth or prevent destruction. For many years, therefore, glucosamine and chondroitin have been considered possible candidates as disease-modifying drugs. Improved understanding of the natural progression of OA has demonstrated that the aetiology and pathophysiology of OA is far more complicated than this. Hyaline cartilage and subchondral bone are in a constant state of degradation and regeneration. Osteoarthritis is accepted to be caused by an imbalance of these anabolic and catabolic processes. An effective disease-modifying drug would need to alter this balance in favour of regeneration, by either promoting anabolic effects or inhibiting catabolic effects. There are many potential therapeutic avenues by which this balance could be modified. These are summarised in *Box 2*, which has been modified from that of Fioravanti and colleagues.¹⁴⁸

In this chapter, we will briefly examine some of the ways in which glucosamine and chondroitin might affect some of these processes with reference to the recent literature.

Glucosamine, chondroitin and hyaline cartilage

As discussed in Chapter 1, glucosamine and chondroitin are contained within hyaline cartilage. The non-collagenous 50% of hyaline cartilage is mainly made up of proteoglycan molecules. These molecules (also called aggrecans) are composed

of long-chain glycosaminoglycans linked to a core protein. Loss of aggrecan from the extracellular matrix in cartilage leads to a change in the biomechanical properties of the tissue, and in so doing accelerates the loss of articular cartilage.

The glycosaminoglycans consist of a hexuronic acid and a hexosamine (amino sugar).

Glucosamine is the hexosamine constituent of keratan sulphate, which is found in hyaline cartilage, alongside the glycosaminoglycans chondroitin 4-sulphate and chondroitin 6-sulphate (which are therefore much larger molecules than glucosamine).⁶³ Chondroitin is a large gel-forming molecule which forms part of cartilage and confers resistance to compression. Despite being a large molecule, it is partially absorbed from the diet or supplements.

Oral bioavailability

Both glucosamine and chondroitin are taken orally, although the dosage advised varies among manufacturers. Clearly, compounds taken by mouth will have no effect if they are not absorbed. There has been some debate about the oral bioavailability of both glucosamine and chondroitin, as such large macromolecules with charge density are not readily absorbed from the gastrointestinal tract.¹⁴⁹

So, before discussing the plausible mechanisms of action of both glucosamine and chondroitin, it is first imperative to determine the pharmacokinetics and bioavailability of both products.

Glucosamine

Laverty and colleagues¹⁵⁰ studied the effects of glucosamine hydrochloride delivered by the nasogastric route on the serum and synovial glucosamine concentrations in eight female horses. The dose given was equivalent to 1500 mg for a 75 kg man. Serum and synovial concentrations were measured before and up to 12 hours post dosing. Pre-dose serum and synovial concentrations were all below measurable levels. After dosing, synovial concentrations ranged from 0.3 µmol/l to 0.7 µmol/l. Serum levels of glucosamine returned to baseline by 6 hours, but synovial concentrations

BOX 2 Possible mechanisms of action for a disease-modifying drug (adapted from Fioravanti 2006¹⁴⁸)

Anabolic effects

- Chondrocyte proliferation without cellular dedifferentiation
- Proteoglycans synthesis
- Collagen type 2 synthesis
- Hyaluronic acid synthesis
- Influence of local growth factors: transforming growth factor (TGF)- β , epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF)
- Effects of sulphate supplementation

Reduction of catabolic effects by:

- Inhibition of the release or the activity of chondrocytic matrix metalloproteinases (MMPs) or negating the downregulation of tissue inhibitors of metalloproteinase (TIMPs)
- Inhibition of the release or the activity of aggrecanases
- Inhibition of cytokines such as interleukin (IL)-1 β , tumour necrosis factor (TNF)- α , etc.
- Inhibition of prostaglandin E2 (PGE2)
- Inhibition of the release or the activity of free radicals of oxygen
- Inhibition of the release or the activity of nitric oxide (NO)
- Inhibition of lysosomal enzymes
- Anti-apoptotic activity
- Anti-inflammatory effect

Mixed effects

- Sulphate supplementation
- Acting as biological response modifiers

remained elevated for up to 12 hours. Adebowale and colleagues¹⁵¹ demonstrated the bioavailability of oral glucosamine hydrochloride and chondroitin sulphate in beagle dogs.

Setnikar and colleagues¹⁵²⁻¹⁵⁶ have extensively studied the absorption, distribution, metabolism and excretion of glucosamine sulphate. Following intravenous administration of radiolabelled glucosamine sulphate in rats, early uptake was seen principally in the liver and kidneys, but there was also early detection in the femoral head articular cartilage, peaking at 0.17 hours post dosing. This uptake by articular cartilage was also shown following oral dosing of radiolabelled glucosamine sulphate in both rat and dog studies.

Using radiolabelled glucosamine sulphate, Setnikar and colleagues¹⁵⁶ studied oral administration in healthy human volunteers, and found gastrointestinal absorption of 90% with bioavailability of 44%. The difference was

due to the hepatic first-pass effect. Biggee and colleagues¹⁵⁷ gave 11 patients with known OA, who had not been taking glucosamine supplements, a single 1500 mg dose of commercial crystalline glucosamine sulphate after an overnight fast. Serum glucosamine levels were measured at baseline and then regularly up to 8 hours post ingestion. Baseline serum glucosamine was undetectable in all subjects. Following ingestion glucosamine was detectable in 17 of the 18 patients. After ingestion, peak levels ranged from 0 to 6.4 $\mu\text{mol/l}$ (mean 3.6 $\mu\text{mol/l}$).¹⁵⁷ Basak and colleagues¹⁵⁸ compared serum values after supplementation with either a novel timed-release capsule or a standard powder-filled one, in a 12-patient multidose randomised crossover study using glucosamine sulphate. Serum glucosamine levels were measured at dosing and up to 24 hours post dosing. Glucosamine was not detected pre-dose, but the peak concentration afterwards was 543.12 ng/ml (\pm 151.16) and 520.98 ng/ml (\pm 152.55) for the powder-filled and timed-release

preparations respectively. They concluded that there was a 21% bioavailability.

Persiani and colleagues¹⁵⁹ measured both plasma and synovial concentrations of glucosamine after 14 days of oral glucosamine sulphate (1500 mg) in 12 OA patients. Glucosamine levels were measured at baseline and at 3 hours following their last dose. After the 2 weeks, a 20.5-fold increase was found in plasma, and a statistically significant 21.5-fold increase in synovial concentrations was observed.

The optimum dose of oral crystalline glucosamine sulphate was examined by Persiani and colleagues.¹⁶⁰ Twelve healthy volunteers received three consecutive daily doses of 750 mg, 1500 mg or 3000 mg in an open randomised, crossover fashion. Plasma levels increased in the dose range 750–1500 mg, but became non-linear at 3000 mg. The blood levels remained elevated for 24 hours after each dose.

Chondroitin

The normal synovial concentration of chondroitin sulphate has been studied in a healthy population group. Nakayama and colleagues¹⁶¹ found that the normal level of synovial chondroitin, in 82 healthy volunteers aged between 20 and 79 years of age, fell with age. The mean synovial concentration was 103.1 nmol/ml for chondroitin 6-sulphate and 18.4 nmol/ml for chondroitin 4-sulphate. The concentration of chondroitin 6-sulphate in the 70–79 years age group was approximately half that of the 20–29 years age group. The ratio of chondroitin 6-sulphate to chondroitin 4-sulphate also steadily decreased with advancing age. Interestingly, it was also noted that females had lower concentrations of synovial chondroitin across all age groups.

Volpi¹⁶² gave 4 g oral chondroitin sulphate (bovine origin) to 20 healthy volunteers and measured plasma levels of chondroitin at baseline and frequently until 48 hours post ingestion. After ingestion, chondroitin sulphate increased significantly, peaking at 2 hours, with plasma levels increased by 200% at 2–4 hours. However, a second, similar, study by Volpi,¹⁶³ using shark chondroitin sulphate, found similar peak levels but at 8.7 hours. The author proposed that the difference may be due to the different molecular weights and charge densities of the two molecules studied.

Technetium-labelled chondroitin sulphate was injected in healthy human volunteers and its whole body distribution was monitored with a gamma

camera. As well as the bloodstream showing very high levels following injection, it was also noted that very high intensity was detected in the area surrounding the knee joints.¹⁶⁴

Ebube and colleagues¹⁶⁵ analysed the different physiochemical and mechanical properties of glucosamine hydrochloride and chondroitin sulphate obtained from various sources. Particle morphology, particle size and other physical properties were found to be greatly variable between sources. This will lead to different bioavailability profiles seen across the product range for both supplements.

There is, therefore, a significant body of evidence supporting the oral bioavailability of both glucosamine and chondroitin products in human *in vivo* studies.

Anabolic state

Many authors have studied the role of glucosamine on both chondrocytes themselves and also the chondroprogenitor cells, such as the human mesenchymal stem cells (hMSCs). Dodge and Jimenez¹⁶⁶ studied the effects of glucosamine sulphate on freshly isolated chondrocytes obtained from patients with knee OA. They observed that 40% of chondrocytes from OA patients failed to respond to glucosamine sulphate. Of the remaining 60%, however, it was observed that the presence of glucosamine sulphate upregulated messenger ribonucleic acid (mRNA) levels of the aggrecan gene in a dose-dependent manner, leading to a corresponding increase in observed levels of aggrecan. They also observed that the presence of glucosamine sulphate decreased matrix metalloproteinase (MMP-3) protein levels as well as enzymatic activity, and increased glycosaminoglycan content.¹⁶⁶

Noyszewski and colleagues¹⁶⁷ have also shown that the addition of radiolabelled glucosamine sulphate to cultured chondrocytes facilitates the production of proteoglycan components with direct uptake of the added radiolabelled glucosamine sulphate.

In another *in vitro* study, Derfoul and colleagues¹⁶⁸ found that addition of 100 μ M glucosamine hydrochloride led to enhanced expression of collagen II and aggrecan, and an increased content of sulphated glycosaminoglycan. It was also observed that the addition of glucosamine partially blocked the effects of interleukin (IL)-1 β on downregulating collagen II and aggrecan

expression. Following addition of glucosamine, the expression of the matrix-degrading enzyme, MMP-13, was also downregulated in both chondrocyte and hMSC cultures.¹⁶⁸

The effects of glucosamine have also been attributed to the upregulation of chondrocyte proliferation, matrix synthesis and gene expression. Varghese and colleagues¹⁶⁹ found that the addition of glucosamine hydrochloride upregulated matrix production in 2D and 3D bovine chondrocyte layers. Up to a dose of 2 mM, this effect was seen principally on aggrecan and type II collagen. This was not seen at higher doses. It was also noted that transforming growth factor (TGF)- β 1 was upregulated in a dose-dependent manner in the presence of glucosamine hydrochloride.¹⁶⁹

Nishimoto and colleagues¹⁷⁰ observed upregulation of the mRNA of collagen II and an increase in aggrecan mRNA expression in porcine chondrocytes after the addition of chondroitin sulphate. However, the effect was not seen with all subtypes of chondroitin sulphate.¹⁷⁰

Mroz and colleagues¹⁷¹ studied whether supplementation of glucosamine to cultured human chondrocytes leads to increased production of chondroitin sulphate. *Figure 16* shows possible pathways.

They concluded that the addition of exogenous H-glucosamine did not stimulate an increased production of chondroitin sulphate.¹⁷¹

Further work by Kim and colleagues¹⁷² explored the anabolic effects of physiological doses of glucosamine sulphate on human osteoblast-like MG-63 cells. The addition of glucosamine sulphate increased alkaline phosphatase (ALP) activity, collagen synthesis, osteocalcin secretion and mineralization of the cultured osteoblastic cells in vitro in a dose-dependent manner from 10–1000 μ g/ml, generally increasing anabolic activity.

Not all studies support an increase in anabolic activity with glucosamine sulphate, however. Using pre-cultured human osteoarthritic explants, Uitterlinden and colleagues¹⁷³ studied the effects of 0.5 mM or 5 mM addition of either glucosamine hydrochloride or glucosamine sulphate. A 5 mM concentration of both glucosamine subtypes was seen to significantly downregulate aggrecan and collagen type II gene expression suggesting inhibited anabolic activity. At the same doses, however, there was also significant anti-catabolic activity with downregulation of MMP-3, and aggrecanase-1. The addition of 0.5 mM glucosamine was not seen to alter either anabolic or catabolic activity at a significant level; however, similar trends were noted when compared with the 5 mM group.¹⁷³

Anticatabolic effects

Piperno and colleagues¹⁷⁴ studied the effects of glucosamine sulphate on proteoglycan synthesis, caseinase, collagenase, and phospholipase

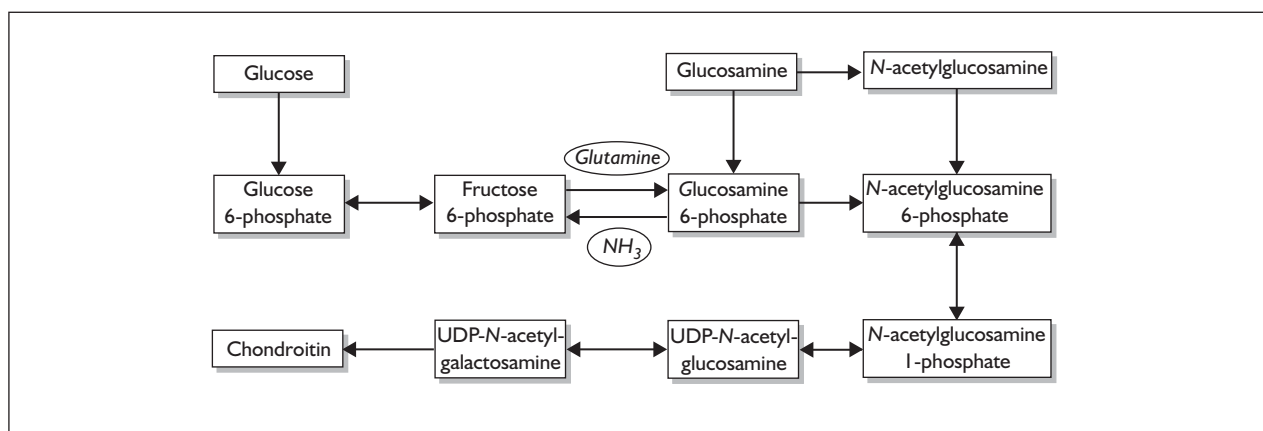


FIGURE 16 Biosynthetic scheme for incorporation of galactosamine into chondroitin from glucose or glucosamine precursors.¹⁷¹ (Reproduced from: Mroz PJ, Silbert JE. Use of 3H-glucosamine and 35S-sulfate with cultured human chondrocytes to determine the effect of glucosamine concentration on formation of chondroitin sulfate. *Arthritis Rheum* 2004;**50**(11):3574–9. Copyright 2004 American College of Rheumatology. Reprinted with permission of John Wiley & Sons, Inc.)

A2 (PLA2), and on production of nitric oxide (NO), cyclic adenosine monophosphate (cAMP), and protein kinase C, in human osteoarthritic chondrocyte cell cultures. Glucosamine sulphate was found to inhibit PLA2 and collagenase activity in a dose-dependent manner. A dose-dependent increase in protein synthesis (minimum concentration 50 µM) and protein kinase C production was seen.

Monfort and colleagues¹⁷⁵ studied the *in vitro* effects of chondroitin sulphate on MMP-3 (stromelysin-1) synthesis in human osteoarthritic chondrocytes. MMP-3 is a cartilage proteolytic enzyme which induces cartilage breakdown and also acts as an inflammatory mediator. Chondrocytes were obtained from human osteoarthritic cartilage from patients of both sexes, over the age of 40 years, who were undergoing arthroplasty. The study noted a marked inhibitory effect of chondroitin sulphate on MMP-3 synthesis at all concentrations tested. No significant differences were found between the various concentrations.¹⁷⁵

The majority of the studies analysing the *in vitro* effects of glucosamine and chondroitin sulphate have focused purely on chondrocyte cultures. The onset of OA is increasingly understood to involve changes within the subchondral bone, including subchondral bone resorption. The balance of bone remodelling factors osteoprotegerin (OPG), and receptor activator of nuclear factor κB ligand (RANKL), are important in this process. Tat and colleagues¹⁷⁶ studied the effects of both glucosamine sulphate and chondroitin sulphate and found that the chondroitin sulphate reduced production of OPG and RANKL, whereas glucosamine sulphate significantly reduced resorptive activity. Both chondroitin sulphate and glucosamine sulphate may, therefore, play an important role in reducing the catabolic effects of subchondral bone in OA.

Cibere and colleagues¹⁷⁷ studied the effects of glucosamine sulphate on type II collagen breakdown in a randomised double-blind placebo-controlled study. One hundred and thirty-seven patients with proven knee OA who had gained at least moderate benefit from glucosamine therapy were randomised to either placebo (discontinuation) or glucosamine (continuation) treatment over a 24-week period. The expectation was that the placebo group would show an increase in type II collagen markers after discontinuation of

glucosamine sulphate. However, this study failed to demonstrate any significant difference between the two groups when measuring glucosamine sulphate degradation products in serum and urine.¹⁷⁷

Aggrecanase activity

The aggrecan degradation simulated by IL-1, tumour necrosis factor (TNF)-α, or retinoic acid is thought largely to be due to the action of aggrecanase. Ilic and colleagues¹⁷⁸ studied the effects of long-term glucosamine on aggrecan degradation in cultures of bovine cartilage. They concluded that a 5 mM concentration of glucosamine indirectly inhibited degradation of aggrecan under simulated catabolic activity. When glucosamine was then removed from the cultures, aggrecanase activity increased. Uitterlinden and colleagues¹⁷³ also demonstrated that the addition of 5 mM either glucosamine sulphate or glucosamine hydrochloride to cultured human osteoarthritic explants demonstrated a significant downregulation of aggrecanase-1. Suppression of aggrecanase-2 was also detected in the glucosamine sulphate group.

Furthermore, work by Sandy and colleagues^{179,180} concluded that aggrecanase activity is significantly decreased in the presence of glucosamine and that this may be via suppression of glycosylphosphatidylinositol-linked proteins.

Inhibition of oxidative stress

As OA is generally (although not exclusively) perceived as an ageing phenomenon, it is postulated that degeneration of articular cartilage and collagen may be a result of oxidative stress. Tiku and colleagues¹⁸¹ explored the hypothesis that glucosamine sulphate and glucosamine hydrochloride may protect collagen from fragmentation secondary to oxidation. Rabbit chondrocytes were cultured and activated with calcium ionophore which induces oxidative metabolism, with the addition of either glucosamine sulphate or glucosamine hydrochloride. The study confirmed that the addition of 25 mM of either glucosamine salts significantly decreased collagen degradation compared with controls. The author concluded that glucosamine was likely to inhibit advanced lipoxidation reactions and therefore prevent oxidation and degradation of collagen matrix.

Anti-inflammatory effects

Several authors have postulated that both glucosamine and chondroitin may function as anti-inflammatory mediators in relation to OA. The anti-inflammatory effects of glucosamine sulphate and chondroitin sulphate on stimulated chondrocyte cell cultures with IL-1 β has been explored. Jomphe and colleagues¹⁸² found that the addition of physiological levels of chondroitin sulphate reduced nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) nuclear translocation, an important transcription factor involved in the initiation of various pro-inflammatory genes such as COX-2, MMP-3 and TNF- α . They also concluded that chondroitin sulphate diminishes IL-1 β -induced increase in other proinflammatory mediators (p38 mitogen activated protein kinase and extracellular signal-regulated kinase $\frac{1}{2}$). Largo and colleagues¹⁸³ also found that physiological doses of glucosamine sulphate inhibit NF- κ B activation in IL-1 β -activated human chondrocytes as well as PGE₂ synthesis. Furthermore, they found that glucosamine sulphate inhibited the expression and synthesis of COX-2, although this result remains controversial within the literature.¹⁵²

Kim and colleagues¹⁷² found that physiological doses of glucosamine sulphate exhibited anti-inflammatory effects on the production of TNF- α , IL-1 β and PGE₂ in macrophage cell lines in vitro.

Inhibition of nitric oxide and prostaglandin E₂ and anti-apoptotic activity

Nitric oxide (NO) is thought to play a role in the pathogenesis of OA. Production of NO is increased in chondrocytes from osteoarthritic bone in comparison with that of normal bone.¹⁸⁴ Nitric oxide production is also thought to be an important factor in the regulation of chondrocyte apoptosis, which in turn is thought to play an important role in the aetiology of OA.¹⁸⁵

Chan and colleagues¹⁸⁶ studied the effects of physiologically relevant concentrations of glucosamine hydrochloride and chondroitin sulphate on the regulation of inflammatory mediators NO and PGE₂. They found that glucosamine hydrochloride, chondroitin sulphate or the combination of both, at clinically relevant doses, reduced mRNA expression of inducible NO synthase (iNOS) at 24 and 48 hours post culture. The combination of both reduced iNOS expression to control levels at 24 hours and 48 hours.

Glucosamine hydrochloride alone significantly reduced iNOS expression at 6 and 24 hours, but not at 48 hours, whereas in contrast, chondroitin sulphate reduced iNOS expression significantly at 48 hours. Synthesis of NO was reduced by both chondroitin sulphate alone and the combination of chondroitin sulphate and glucosamine hydrochloride at 24 hours. Furthermore Chan and colleagues¹⁸⁷ showed the downregulation of inflammatory mediators PGE₂, NO, iNOS, MMP-3 and aggrecanase-2 in IL-1 β -stimulated bovine cartilage explants in the presence of glucosamine hydrochloride and chondroitin sulphate.¹⁸⁷ The upregulation of COX-2 with the addition of IL-1 β was abrogated with the addition of chondroitin sulphate and glucosamine hydrochloride. They also found that upregulation of tissue inhibitor of metalloproteinase-3 transcripts was seen with the addition of both glucosamine hydrochloride and chondroitin sulphate.

Huser and Davies¹⁸⁸ demonstrated that a lipophilic derivative of glucosamine, Glu5, is able to prevent impact-induced chondrocyte death, possibly by reducing mitochondrial depolarisation following a single impact load in vitro. Jomphe and colleagues¹⁸² studied the effects of the addition of chondroitin sulphate to rabbit chondrocytes stimulated with sodium nitroprusside, a compound known to induce apoptosis, and found that the addition of chondroitin sulphate protected the chondrocytes from apoptosis to the same level as the group that was not exposed to sodium nitroprusside. Caraglia and colleagues¹⁸⁹ also showed that osteoarthritic mice models who were treated with chondroitin sulphate prior to being sacrificed, showed a significant reduction in chondrocyte apoptosis. Interestingly, this effect was increased when they were treated with both chondroitin sulphate and mud therapy with sulphur mineral water.

Biological response modifiers

It has also been suggested that both glucosamine and chondroitin may act as biological response modifiers (BRMs) for chondrocytes under simulated conditions of stress. A BRM is an agent which promotes the defence of the host against multiple stresses. Lippiello¹⁹⁰ studied the effects of the addition of glucosamine and chondroitin to bovine cartilage explants which were subject to various stressors, including mechanical stress, heat, enzyme-induced matrix depletion and cytokine stress. The study concluded that both glucosamine hydrochloride and chondroitin

sulphate modulate the protective metabolic response in favour of repair and regeneration at doses in keeping with the bioavailability of these agents. Interestingly, they also concluded that cartilage explants from older animals were more likely to undergo metabolic change with stress, but also have a greater response to the addition of glucosamine hydrochloride and chondroitin sulphate. Nerucci and colleagues¹⁹¹ also found that human chondrocyte cultures exposed to a simulated pressurisation cycle with the addition of IL-1 β showed a significant decrease in proteoglycan concentration compared with controls (without IL-1 β) at day 10 of culture. This decrease was significantly reduced with the presence of chondroitin sulphate at 10 μ g/ml and 100 μ g/ml.

Sulphate deficiency

A further plausible hypothesis is based on the role of the sulphated amino sugars found in glucosamine hydrochloride and chondroitin sulphate. Cartilage contains tissue-specific glycosaminoglycans that require a source of inorganic sulphate for its synthesis. Although the recommended dietary allowance has previously been derived in young healthy individuals, this does not take into account the increased turnover of glycosaminoglycans during the osteoarthritic process. Furthermore, many patients with OA take paracetamol as a simple analgesic to manage their symptoms. Paracetamol is largely metabolised by sulphation and indeed 40% of paracetamol is excreted in urine conjugated with sulphate, which may contribute to sulphate deficiency. It has been previously shown that sulphate depletion inhibits glycosaminoglycans synthesis *in vitro* in rat and human articular cartilage. Indeed, human cartilage is thought to be particularly sensitive to sulphate deficiency.^{192,193}

Hoffer and colleagues¹⁹⁴ have also investigated the role of sulphate as the proposed mechanism of action of glucosamine sulphate. They first studied whether oral glucosamine sulphate increases serum sulphate concentrations. They then investigated whether this increase was also found within synovial fluid. Finally, the group studied whether the use of paracetamol affected the serum sulphate response to glucosamine sulphate. Seven healthy adults had venous blood measured for sulphate levels before, and then 3 hours following, ingestion of 1 g glucosamine sulphate (1.65 mmol sulphate). The study was then repeated in a similar fashion with the addition of 1 g paracetamol along with

the glucosamine sulphate. In a separate group, 15 patients with known OA, who were to undergo diagnostic needle aspiration in the outpatient setting, consented to the measurement of both synovial and serum sulphate. This was to investigate the relationship between serum and synovial sulphate levels which were found to be virtually identical.

Of the seven healthy patients, the mean baseline serum sulphate level was 331 μ mol/l which increased to 375 μ mol/l 3 hours following ingestion of glucosamine sulphate. In the glucosamine sulphate and paracetamol group, the baseline level decreased from 325 μ mol/l to 290 μ mol/l at 3 hours. The study therefore concluded that glucosamine sulphate increases serum inorganic sulphate concentration in normal individuals and that this increase is reversed by coingestion of paracetamol.¹⁹⁴

Cordoba and Nimni¹⁹⁵ investigated the relationship between dietary levels of protein and urinary excretion of sulphate. This study assessed whether consumption of chondroitin sulphate and glucosamine sulphate increased urinary excretion of sulphate. Healthy human volunteers were instructed to record their dietary intake. Patients were separated into five groups depending on their routine dietary protein intake. In the two lowest groups for dietary protein intake, consuming 15 mM or less of sulphur over 24 hours, supplementation with chondroitin sulphate did not lead to the expected increase in urinary secretion, suggesting retention of sulphate, presumably due to dietary insufficiency. In the groups consuming 25 mM or more of sulphur, supplementation of either glucosamine sulphate or chondroitin sulphate led to an increase in urinary excretion of sulphate over the measured daily dietary consumption. The effect of glucosamine sulphate for patients with low dietary sulphur was not described in the paper. It is plausible, therefore, that chondroitin sulphate and glucosamine sulphate supplementation may be most effective in patient populations with low dietary sulphur, such as vegetarians or those who consume little red meat.

Summary

While much of the evidence presented above is derived from *in vitro* experiments which may not reflect the osteoarthritic human knee, there are a number of plausible mechanisms by

which glucosamine, chondroitin or the sulphate component of the treatments may act:

- Bioavailability: there was significant evidence that oral supplements of both chondroitin and glucosamine led to an increase in both serum and synovial fluid concentrations.
- Anabolic effect: in vitro studies supported some anabolic function for glucosamine.
- Catabolic effect: there was a stronger evidence base for inhibition of catabolism.

- Sulphate effect: there was evidence to support the intriguing hypothesis that it may be the sulphate rather than the glucosamine which has the effect.

The exact mechanism(s) of either drug is as yet unknown. Furthermore, many but not all of the in vitro studies utilised concentrations in excess of those found from the bioavailability studies, and therefore may not be clinically relevant.

Chapter 6

Discussion and recommendations

Summary of findings

In this review we set out to address a series of questions with regard to the clinical effectiveness and cost-effectiveness of glucosamine and chondroitin.

- *Does glucosamine prevent or slow progression of OA of the knee?*
 - There was evidence that the Rotta powdered oral preparation of glucosamine sulphate reduced joint space loss and may even improve joint space width after 3 years of therapy when compared with placebo. The clinical significance of joint space narrowing and changes in width over time were less certain. Absolute joint space width is a poor predictor of outcomes in terms of either QoL or need for knee arthroplasty. There is, however, some evidence that changes in joint space width do relate to clinical outcomes such as the need for future knee arthroplasty.
 - There was evidence that glucosamine had a beneficial impact on long-term outcome of knee arthroplasty (6.3% in the treated group versus 14.5%); an effect seen despite small numbers and the opportunity for substantial treatment group switching during follow-up which would, if anything, lessen the observed difference between the two study groups.
 - A small statistically significant improvement was observed in QoL measured using WOMAC in the treated group versus the placebo group.
- *Does chondroitin prevent or slow progression of OA of the knee?*
 - We found evidence to support the conclusion that chondroitin had a small effect on structural changes, but this time there was no corroborating evidence of a translation of this finding into long-term clinically important outcomes. The impact on QoL appeared to be influenced by the tool used and was inconsistent between studies.
- As there was currently no way to determine what, if any, significance joint space width has on QoL, health utility or long-term outcomes, it was not possible to draw any conclusions about the clinical effectiveness of chondroitin.
- *Does the combination of both offer any greater effect?*
 - While a few studies did use combination therapy, the comparison was placebo not single therapy. It was not possible, therefore, to address whether there was a relatively greater gain with such a combination.
- *If they are useful, what dosages should be used?*
 - With only two trials for the one preparation for which we had concluded that there was evidence of effectiveness, and with both trials using identical dosing regimens, it was not possible to address the question of what was the optimal dose. It is worth noting that both trials used the Rotta glucosamine product and were sponsored by the pharmaceutical company.
- *What are the costs, in terms of both cost of the products and any side effects?*
 - The reported adverse event profile for glucosamine sulphate was unremarkable. The only potential issue identified from data beyond clinical trials was an interaction with warfarin. The one death associated with acute liver failure, however, highlighted the need for long-term monitoring of the use of glucosamine and that, to date, experience from formal study of the treatment draws on a relatively small patient pool. There is no licensed preparation of glucosamine sulphate available in the UK. Over-the-counter preparations vary substantially in cost and content. For modelling, the cost of the licensed glucosamine hydrochloride product was taken as a marker for the likely price to the NHS of a sulphate licensed product should one become available (BNF price of £18.40).

- *Are there any savings to the NHS from their use, for example by reduced consumption of prescribed non-steroidal anti-inflammatory drugs, or from avoidance of knee arthroplasty?*
 - There was little evidence from the trials that glucosamine sulphate reduced the need for oral analgesia, but as noted above, the long-term follow-up data did support a reduction in the need for knee arthroplasty.
- *Is there evidence of cost-effectiveness from well constructed economic evaluations?*
 - We did not identify any economic evaluations focusing on the long-term cost-effectiveness of glucosamine sulphate. Our own analysis estimated the cost per QALY to be £21,335. Gains in cost to the health service were accompanied by modest health-related gains. However, sensitivity analysis suggested that the cost-effectiveness of glucosamine sulphate was largely dependent on the magnitude of QoL gains from therapy. The estimates of cost-effectiveness were imprecise and suggest some degree of decision uncertainty.
 - From our review we conclude that the evidence is inconclusive, but suggestive enough of benefit to justify further research for glucosamine sulphate. Our conclusions are in keeping with those of the recent NCCCC guidelines¹ that included an assessment of glucosamine and chondroitin. While they did not focus on long-term outcomes and used a different methodology for determining utility scores in the economics analysis, they did report that a small effect was observed for glucosamine sulphate on QoL measures and joint space. Like us, they concluded from their economic analysis that evidence of cost-effectiveness was not conclusively established.

Similarly authors of the systematic reviews included in our clinical effectiveness review reported evidence of some clinical effect associated, in particular, with preparations of glucosamine sulphate, and to some extent, chondroitin.

- *Are the alleged benefits of glucosamine on knee cartilage biologically plausible?*
 - Bioavailability of the glucosamine in the synovial fluid has been demonstrated.

While a specific mechanism of action has not been established, evidence for a number of potential actions on the joint has been observed for glucosamine, chondroitin and sulphate (in vitro, in animals and in healthy volunteers).

- *If, as suggested by the commissioning brief, the evidence suggests that there is no gain in short-term symptom relief, but only in long-term preservation of cartilage (which does imply longer-term reductions in symptoms, advanced OA and perhaps the need for knee arthroplasty), what should the comparator in trials be?*
 - Because OA is now recognised to be a condition that is not necessarily relentlessly progressive and, in fact, the symptoms experienced by individuals can range widely, a comparator group is essential for the interpretation of trial data. NCCCC identified, in their review of treatments for OA of the knee, that none of the existing therapies have been shown to alter the clinical course of the condition. The comparator, therefore, has to be against placebo.
- *If the gain is in long-term outcomes, are there short-term indicators of benefit which could be used, rather than waiting 20 years for advanced OA to become manifest? Joint space narrowing on plain film has been used as one outcome. Could more complex forms of imaging, such as MRI, positron emission tomography, computerised tomography, other radionuclide techniques or ultrasound, provide more detailed assessment of the quality and thickness of remaining cartilage, and hence give earlier confirmation of benefit?*
 - The two most significant challenges around imaging the knee using X-ray have been the difficulty in relating changes in the image to long-term outcomes and the need to use quantitative measures to assess change.
 - There have been growing numbers of reports in the literature about the use of other imaging techniques in assessing joint space changes in OA. While there is evidence of a change in joint space being associated with long-term outcomes such as knee arthroplasty, regardless of the technique used to image the joint, the difficulties remain about the reliability of such measurements. MRI and other techniques afford the additional benefit of providing more information about

structural changes within the joint itself. An evidence-driven consensus conference in 2006 led by OMERACT and OARSI attempted to summarise opinion about the most potentially useful features derivable from MRI. They concluded that articular cartilage loss, osteophytes, bone marrow abnormalities, synovitis, meniscal abnormalities and synovial effusions held the greatest promise. Despite enthusiasm for these new measures, the need for long-term cohorts and follow-up data was recognised as a priority to determine the clinical significance.

- *Which variables or assumptions (e.g. costs, QoL, mortality, extrapolation of effectiveness over time) are most important in generating uncertainty in the cost-effectiveness estimates, and which would provide the greatest return in terms of reducing uncertainty at reasonable cost? These variables and assumptions will be identified using value of information analysis, and will form the main basis in recommendations for further research.*
 - Value of information analysis indicated that further research to reduce uncertainty would be beneficial. Greatest uncertainty around costs is generated by the uncertainty around the probability and cost of knee arthroplasty. The most important driver in QALY variability is uncertainty around the QoL gain associated with treatment. Overall, variability in cost-effectiveness is most heavily determined by uncertainty regarding the magnitude and duration of QoL gains following treatment.

For chondroitin, biologically plausible mechanisms have been reported, but the clinical effectiveness evidence was less convincing with greater heterogeneity in conclusions. Trials of chondroitin, however, have tended to be of poorer quality, so uncertainties about the clinical effects of chondroitin remain.

Challenges for clinical effectiveness

Despite numerous reviews of these two treatments, most conclusions have previously been driven by short-term findings, particularly for measures of symptoms and function. The failure to undertake subgroup analysis by duration of follow-up made it impossible to determine the effectiveness for long-term outcomes. Studies including structural

outcomes tended to be longer term; therefore, the conclusions of previous reviews on this outcome are of relevance. Poolsup and colleagues⁷³ focused on long-term outcomes and identified two of the three trials we included. Their conclusions were similar to ours, supporting evidence of clinical effectiveness for both symptoms and structural outcomes. Towheed and colleagues⁶² included two of the three trials we included in their assessment of structural outcomes, plus an additional shorter-duration study that we excluded. They were cautious in their interpretation of the significance of the surrogate end point of joint space change and at that time did not have access to the longer follow-up information about knee arthroplasty.

Surrogate end points in trials are widely used for many conditions and often lead to concerns regarding their translation into long-term effects. As a surrogate end point, joint space narrowing has been approved as an acceptable trial outcome measure for OA by OMERACT and regulatory bodies⁴¹ but its insensitivity in diagnosis, measuring disease activity and assessing progression has been noted.

To address the challenges of surrogate end points in technology assessment, the HTA are currently establishing a working group to explore the challenges of surrogate markers in clinical trials with a view to preparing guidance on their use in health technology assessment. Critical to our interpretation of the potential effectiveness of glucosamine sulphate has been the evidence of a translation from the surrogate end point of joint space narrowing to the clinical end point of knee arthroplasty.

Where evidence of effectiveness was observed (for glucosamine sulphate) the conclusions are based on only three trials. While two of the three trials were well designed, they followed similar treatment protocols and therefore did not allow any assessment of the relative merits of different doses, products or regimens.

Other challenges included interpretation of QoL measures. A number of different tools were used to assess pain, function and disability. Authors rarely stated a priori expectations of what might represent a clinically important change. There was little information about the long-term natural history of such measures or how such measures relate to other outcomes, including knee arthroplasty or other service utilisation.

Finally, none of the studies were undertaken in the UK and, given the importance of access to services and complexity of decision-making around the timing of surgical intervention, generalisability to the UK health-care setting is difficult.

Challenges for modelling

Three main challenges for modelling are worth noting. First, the lack of robust epidemiological and service utilisation data for the UK meant that there was substantial uncertainty about the generalisability of trial data and the cost of 'current care'. Second, there was no direct measure of a generic preference-based QoL measure (such as HUI3, SF-6D, EQ-5D) and as a result mapping formulae had to be used to map WOMAC to a utility measure. Finally, the economic model relied on the results of two studies for effect of treatment on WOMAC and knee arthroplasty. The number of participants was relatively small, and only one treatment protocol and glucosamine preparation was used. There remain, therefore, a number of decision uncertainties that could not be addressed in the economic modelling.

Research needs

- Based on sensitivity analysis and value of information analysis, three research priorities were identified:
- Quality of life – further clarification of the potential QoL gains from treatment with glucosamine sulphate versus placebo over long-term treatment would reduce uncertainty in the cost-effectiveness estimates. There was consistent evidence of some effect on various composite scores, but no study utilised a generic preference-based QoL measure (such as HUI3, SF-6D, EQ-5D) that can readily be used to estimate utility. Any future trial should also inform our understanding of the relationship between QoL and costs collecting resource use and cost data to allow estimation of the resource impact of any changes in QoL.
- Structural outcomes – further long-term trial data are required to clarify the impact on the ultimate need for knee arthroplasty, including the ability to delay the need for surgery. As joint replacements have a finite lifespan, optimising the timing of surgery is a critical

aspect of decision-making for surgeons, and treatments that delay the need for arthroplasty may also reduce the need for subsequent revision surgery. As yet, surrogate marks continue to be proposed, but in the absence of long-term follow-up to surgery, the implications of change in surrogate end points remain uncertain.

- Knee arthroplasty – a nationally representative cohort study is required to understand what proportion of patients with OA (diagnosed in primary care and referred to secondary care) require knee arthroplasty.

Trials of interventions should focus on glucosamine sulphate and the Rotta product is the only product to date that has demonstrated effectiveness. While uncertainty about other preparations remains, there was insufficient evidence of effectiveness and it was not possible to develop an economic case for further study at this time. Any trial should:

1. include collection of information about co-prescribing, the use of other interventions and adverse events
2. recruit obese and overweight participants and people across stages of OA severity
3. use the opportunity to gather a number of measures of joint structure and damage
4. be of at least 3 years' follow-up with a mechanism to follow the cohort long term (e.g. through record linkage to hospital data).

In preparing the background and undertaking the clinical effectiveness review and economics modelling, it was apparent that there was a lack of information about the epidemiology, management and natural history of OA of the knee in the UK. Greater understanding of the incidence and prevalence in the community, as presenting to primary care and as referred to specialist services, would benefit any future technology assessment in this clinical area. Alongside this, information about current care should be obtained. Some of this information could be obtained using routine primary care databases, but would require supplementation to estimate the impact in the community and in secondary care.

A number of studies noted that expectations, coping and tolerance of symptoms varied between individuals and had substantial impacts on their utilisation of services. Further research to understand the impact of such patient factors

would help in the planning of services and target need (versus demand).

The biological mechanism of glucosamine sulphate and chondroitin remains uncertain. In particular, the proposal that the active substance may be sulphate should be explored further. Other sulphate-rich supplements might provide a useful comparator, e.g. glutathione and L-methionine. Paracetamol, metabolised by sulphation may potentially lead to sulphate deficiency, and therefore a better understanding of this potential mechanism has important clinical implications. Most work has focused on the effect of compounds on the chondrocyte and cartilage. Further work is needed to explore the impact on subchondral bone, which is increasingly seen as the primary disease initiator.

Conclusion

There was evidence that glucosamine sulphate shows some clinical effectiveness in the treatment of OA of the knee. Cost-effectiveness was not conclusively demonstrated, but substantial uncertainty was observed for some key determinants in the model. There was evidence from biological studies to support the potential clinical impact of glucosamine sulphate. For other preparations, the evidence base was less consistent (chondroitin) or absent (glucosamine hydrochloride).

Further research to reduce uncertainty and confirm the impact on surgical outcomes in a UK clinical setting would be beneficial.



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Contribution of authors

Corri Black (Senior Clinical Lecturer) led the review and drafted the final report. Christine Clar (Systematic Reviewer) led the review of clinical effectiveness and drafted this chapter.

Rob Henderson (Consultant in Public Health Medicine) drafted sections of the background. Campbell MacEachern (Specialist Registrar) drafted sections of the background and the chapter on biological plausibility. Paul McNamee (Senior Research Fellow) and Zahidul Quayyum (Research Fellow) undertook the cost-effectiveness analysis and drafted this section. Pam Royle (Senior Research Fellow) developed the search strategy and undertook all searching. Sian Thomas (Systematic Reviewer) data extracted and contributed to the draft clinical effectiveness chapter. All authors read and commented on the final draft.



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Appendix I

Search strategies

Main search

EMBASE 1996 to 2007 week 43

Search terms	No. of hits
1 exp Chondroitin/	467
2 chondroitin.tw.	3604
3 1 or 2	3820
4 exp Glucosamine/	1792
5 glucosamine.tw.	2799
6 4 or 5	3468
7 3 or 6	6899
8 exp Osteoarthritis, Knee/	4582
9 (osteoarthritis adj3 knee\$.tw.	2463
10 8 or 9	5021
11 7 and 10	250
12 limit 11 to English language	213

Ovid MEDLINE 1996 to October week 3 2007

Search terms	No. of hits
1 exp Chondroitin/	2620
2 chondroitin.tw.	3863
3 1 or 2	4765
4 exp Glucosamine/	2655
5 glucosamine.tw.	2920
6 4 or 5	4373
7 3 or 6	8800
8 exp Osteoarthritis, Knee/	4159
9 (osteoarthritis adj3 knee\$.tw.	2406
10 8 or 9	4818
11 7 and 10	150
12 limit 11 to English language	125

AMED (Allied and Complementary Medicine) 1985 to October 2007

Search terms	No. of hits
1 (glucosamine or chondroitin).mp. [mp=abstract, heading words, title]	53

Repeat search strategies in MEDLINE and EMBASE for high specificity for systematic reviews or RCTs on chondroitin or glucosamine for osteoarthritis.

Ovid MEDLINE 1996 to October week 4 2007

1 (glucosamine or chondroitin).mp.

2 osteoarthritis.mp.
3 1 and 2
4 randomized controlled trial.pt.
5 random\$.tw.
6 meta-analysis.pt.
7 (meta-analysis or systematic review).tw.
8 4 or 5 or 6 or 7
9 3 and 8
Total number of hits = 101.

EMBASE 1996 to 2007 week 43

1 (glucosamine or chondroitin).mp.
2 osteoarthritis.mp.
3 1 and 2
4 random\$.tw.
5 (meta-analysis or systematic review).tw.
6 4 or 5
7 3 and 6
Total number of hits = 108.

Cochrane Library issue 3 2007

1 (osteoarthritis and knee):ti,ab,kw
2 (chondroitin):ti,ab,kw or (glucosamine):ti,ab,kw
3 1 and 2
Total number of hits = 77.

Additional searches

SCI meeting abstracts only (14/11/2007)

TS=((glucosamine or chondroitin) and (osteoarthritis or knee))
DocType=Meeting Abstract OR Meeting Summary OR Meeting-Abstract; Language=All languages; Database=SCI-EXPANDED; Timespan=1970-2007

Websites

ACNFP – Advisory Committee on Novel Foods and Processes: www.acnfp.gov.uk/assess/fullapplies/glucosamine
Food Standards Agency: www.food.gov.uk/news/newsarchive/2007/sep/glucosamine
US Food and Drug Administration – Center for Food Safety and Applied Nutrition (CFSAN): www.cfsan.fda.gov/~dms/qhcosteo.html
European Food Safety Authority (EFSA): www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_home.htm
No documents found.

Searches for adverse effects of glucosamine and chondroitin

Ovid MEDLINE 1950 to March week 4 2008

Search terms

	No. of hits
1 exp Chondroitin/ae [Adverse Effects]	129
2 exp Glucosamine/ae [Adverse Effects]	144
3 exp Chondroitin/	7783
4 exp Glucosamine/	11,072
5 3 or 4	18,390
6 (risk or safety or adverse or harm or interaction\$or pharmacovigilance).m_titl.	332,967
7 5 and 6	429
8 1 or 2 or 7	672

EMBASE 1980 to 2008 week 13

Search terms

	No. of hits
1 exp Chondroitin/	651
2 exp Glucosamine/	2649
3 1 or 2	3089
4 (risk or safety or adverse or harm or interaction\$or pharmacovigilance).m_titl.	275,151

5 3 and 4	87
6 exp Chondroitin/ae [Adverse Drug Reaction]	21
7 exp Glucosamine/ae [Adverse Drug Reaction]	118
8 6 or 7	123
9 5 or 8	199

AMED (Allied and Complementary Medicine) 1985 to March 2008

((chondroitin or glucosamine) and (adverse or safety or harm* or pharmacovigilance or risk* or interaction* or side-effect*)) = 26 retrieved.

ISI Web of Science and ISI

Proceedings 1980 to March 2008

((chondroitin or glucosamine) and (adverse or safety or harm* or pharmacovigilance or risk* or interaction*)) = 125 retrieved

Additional websites searched

- UKMI (www.ukmi.nhs.uk/)
- FDA (www.fda.gov/)
- MHRA (www.mhra.gov.uk/index.htm).

Appendix 2

Table of excluded reviews

Review	Reason for exclusion
AHRQ 2007 ²	No outcomes regarding joint structure assessed; high quality review, but mainly a review of systematic reviews
Ameye 2006 ¹⁹⁶	Review of functional nutritional ingredients targeting osteoarthritis; glucosamine and chondroitin sulphate excluded
Biggee 2004 ¹⁹⁷	Not a systematic review
Bjordal 2007 ¹⁹⁸	Only short-term data reported; main data were reported for up to 4 weeks; the longest follow-up reported for 12 weeks
Clayton 2007 ¹⁹⁹	Not a systematic review
Distler 2006 ²⁰⁰	Not a systematic review
Felson 2000 ²⁰¹	Not a systematic review
Leeb 2000 ²⁰²	No outcomes regarding joint structure assessed
Lozada 2007 ²⁰³	Not a systematic review
Matheson 2003 ²⁰⁴	Not a systematic review (some information on search strategy, but no other methodology described)
McAlindon 2000 ²⁰⁵	No outcomes regarding joint structure assessed
McAlindon 2001 ²⁰⁶	Not a systematic review (summary of McAlindon 2000 ²⁰⁵)
McAlindon 2005 ²⁰⁷	Not a systematic review
McAlindon 2007 ²⁰⁸	Not a systematic review (comment on Reichenbach 2007 ⁶¹)
Reginster 2007 ²⁰⁹	Not a systematic review
Towheed 2007 ²¹⁰	Not a systematic review
Vlad 2007 ²¹¹	No outcomes regarding joint structure assessed
Zerkak 2004 ²¹²	Not a systematic review

AHRQ, Agency for Healthcare Research and Quality.

Appendix 3

Results of meta-analyses in the systematic reviews

Study	Outcome	n ^a	Effect measure	Results of meta-analyses
Glucosamine Structure				
Poolsup 2005 ⁷³	Disease progression (joint space narrowing > 0.5 mm)	2	Relative risk	0.46 (95% CI 0.28 to 0.73, p = 0.0011)
Richy 2003 ⁷⁵	Minimum joint space narrowing (JSN) (only glucosamine studies included in this category)	2	Risk difference	-0.12 (95% CI -0.05 to -0.19, p = 0.0006)
			NNT	9 (95% CI 6 to 20)
Towheed 2005 ⁶²	Mean joint space width, glucosamine vs placebo	1	Standardised mean difference (fixed-effects model)	0.07 (95% CI -0.20 to 0.34, p = NS)
			Standardised mean difference (fixed-effects model)	0.24 (95% CI 0.04 to 0.43, p = 0.02)
Pain				
Poolsup 2005 ⁷³	WOMAC pain subscale	2	Effect size (standardised mean difference)	0.41 (95% CI 0.21 to 0.60, p < 0.0001)
Towheed 2005 ⁶²	Pain (VAS), glucosamine vs placebo	15	Standardised mean difference (random-effects model)	-0.61 (95% CI -0.95 to -0.28, p = 0.0003)
			Standardised mean difference (fixed-effects model)	-0.04 (95% CI -0.17 to 0.09, p = NS)
Function				
Poolsup 2005 ⁷³	WOMAC function subscale	2	Effect size	0.46 (95% CI 0.27 to 0.66, p < 0.0001)
			Global effect size	0.30 (95% CI 0.11 to 0.49, p < 0.001)
Richy 2003 ⁷⁵	Lequesne index, glucosamine vs placebo	4	Standardised mean difference (random-effects model)	-0.51 (95% CI -0.96 to -0.05, p = 0.03)
			Relative risk (fixed-effects model)	1.52 (95% CI 1.20 to 1.91, p = 0.0005)
Towheed 2005 ⁶²	WOMAC stiffness subscale, glucosamine vs placebo	5	Standardised mean difference (fixed-effects model)	-0.06 (95% CI -0.23 to 0.11, p = NS)
			Standardised mean difference (fixed-effects model)	-0.07 (95% CI -0.21 to 0.08, p = NS)
Towheed 2005 ⁶²	WOMAC function subscale, glucosamine vs placebo	6	Standardised mean difference (fixed-effects model)	-0.15 (95% CI -0.30 to 0.00, p = NS)
			Standardised mean difference (fixed-effects model)	-0.15 (95% CI -0.30 to 0.00, p = NS)

Study	Outcome	n ^a	Effect measure	Results of meta-analyses
Adverse events				
Poolsup 2005 ⁷³	Any adverse events	2	Relative risk	1.02 (95% CI 0.93 to 1.11, <i>p</i> =NS)
Towheed 2005 ⁶²	Number of patients reporting adverse events, glucosamine vs placebo	11 (14)	Relative risk (fixed-effects model), three studies with no events	0.97 (95% CI 0.88, 1.08, <i>p</i> =NS)
	Withdrawals due to adverse events, glucosamine vs placebo	9 (17)	Relative risk (fixed-effects model), eight studies with no events	0.82 (95% CI 0.56 to 1.21, <i>p</i> =NS)
Chondroitin				
Structure				
Bana 2006 ⁷⁴	Mean/minimum joint space width	3	Data summarised narratively, no meta-analysis	Preservation of joint space suggested, but significance unclear
Reichenbach 2007 ⁶¹	Minimum joint space width	5	Effect size (Cohen)	0.16 mm (95% CI 0.08 to 0.24)
	Mean joint space width	5	Effect size (Cohen)	0.23 mm (95% CI 0.09 to 0.37)
Pain				
Reichenbach 2007 ⁶¹	Joint pain [VAS (global, on activity), WOMAC pain subscale]	20	Effect size (based on differences of means and pooled SDs)	-0.75 (95% CI -0.99 to -0.50), equivalent to a difference in pain scores of 1.6 cm on a 10cm VAS scale
Bana 2006 ⁷⁴	VAS pain	6	Effect size (Cohen)	0.60 (95% CI 0.26 to 0.94)
Function				
Bana 2006 ⁷⁴	Lequesne index	5	Effect size (Cohen)	0.57 (95% CI 0.26 to 0.88)
	Being a responder	4	Relative risk	1.83 ± 0.34
Adverse events				
Bana 2006 ⁷⁴	Tolerance	7		All studies concluded on a good to excellent tolerability
Reichenbach 2007 ⁶¹	Any adverse events	12	Relative risk	0.99 (95% CI 0.76 to 1.31)
	Patients withdrawing because of adverse events	9	Relative risk	0.98 (95% CI 0.64 to 1.52)
	Serious adverse events	2	Relative risk	1.52 (95% CI 0.12 to 19.97)

continued

Study	Outcome	n ^a	Effect measure	Results of meta-analyses
Glucosamine/chondroitin				
<i>Structure</i>				
<i>Pain</i>				
Richy 2003 ⁷⁵	VAS pain	12	No data reported	
<i>Function</i>				
Richy 2003 ⁷⁵	Lequesne index	10	Global effect size	0.45 (95% CI 0.33 to 0.57, $p < 0.001$)
Richy 2003 ⁷⁵	Mobility	3	Global effect size	0.43 (95% CI 0.32 to 0.54, $p < 0.001$)
Richy 2003 ⁷⁵	Being a responder (vs placebo, based on dichotomisation by investigator or global assessment)	9	Global effect size	0.59 (95% CI 0.25 to 0.92, $p < 0.001$)
			Relative risk	1.59 (95% CI 1.39 to 1.83, $p < 0.001$)
<i>Adverse events</i>				
Richy 2003 ⁷⁵	Any adverse events	11	Absolute risk difference NNT	20% (95% CI 15% to 26%) 4.9
			Relative risk	0.80 (95% CI 0.59 to 1.08, $p = 0.15$)

NNT, number needed to treat; NS, not significant; VAS, visual analogue scale.
^a *n* refers to number of studies included in the meta-analysis.

Appendix 4

Results of meta-analyses – subgroup and sensitivity analyses

Study	Outcome	Factor	n	Results
Glucosamine Towheed 2005 ⁶²	Minimum joint space width	Allocation concealment adequate, glucosamine vs placebo	2	Standardised mean difference (fixed-effects model): 0.24 (95% CI 0.04 to 0.43, $p = 0.02$)
	Pain (VAS)	Allocation concealment adequate, glucosamine vs placebo	8	Standardised mean difference (random-effects model): -0.19 (95% CI -0.50 to 0.11, $p = NS$)
	Pain (VAS)	Glucosamine preparation	7 Rotta, 8 non-Rotta	Standardised mean difference (random-effects model): Rotta -1.31 (95% CI -1.99 to -0.64, $p = 0.0001$); non-Rotta -0.15 (95% CI -0.35 to 0.05, $p = NS$)
	WOMAC pain subscale	Allocation concealment adequate, glucosamine vs placebo	7	Standardised mean difference (fixed-effects model): -0.04 (95% CI -0.17 to 0.09, $p = NS$)
	WOMAC pain subscale	Glucosamine preparation	2 Rotta, 5 non-Rotta	Standardised mean difference (fixed-effects model): Rotta -0.10 (95% CI -0.29 to 0.09, $p = NS$); non-Rotta 0.01 (95% CI -0.16 to 0.17, $p = NS$)
	Lequesne index	Allocation concealment adequate, glucosamine vs placebo	3	Standardised mean difference (random-effects model): -0.61 (95% CI -1.21 to -0.01, $p = 0.05$)
	Lequesne index	Allocation concealment adequate, glucosamine vs placebo	1	Relative risk (fixed-effects model): 1.43 (95% CI 1.08 to 1.91, $p = 0.01$)
	Lequesne index	Glucosamine preparation	4 Rotta	Standardised mean difference (random-effects model): -0.51 (95% CI -0.96 to -0.05, $p = 0.03$)
	WOMAC stiffness subscale	Allocation concealment adequate, glucosamine vs placebo	2 Rotta	Relative risk (fixed-effects model): 1.52 (95% CI 1.20 to 1.91, $p = 0.0005$)
	WOMAC stiffness subscale	Glucosamine preparation	5	Standardised mean difference (fixed-effects model): -0.06 (95% CI -0.23 to 0.11, $p = NS$)
	WOMAC function subscale	Allocation concealment adequate, glucosamine vs placebo	1 Rotta, 4 non-Rotta	Standardised mean difference (fixed-effects model): Rotta -0.22 (95% CI -0.50 to 0.06, $p = NS$); non-Rotta 0.04 (95% CI -0.18 to 0.25, $p = NS$)
	WOMAC function subscale	Glucosamine preparation	6	Standardised mean difference (fixed-effects model): -0.07 (95% CI -0.21 to 0.08, $p = NS$)
	WOMAC total	Allocation concealment adequate, glucosamine vs placebo	2 Rotta, 4 non-Rotta	Standardised mean difference (fixed-effects model): Rotta -0.14 (95% CI -0.34 to 0.05, $p = NS$); non-Rotta 0.03 (95% CI -0.18 to 0.25, $p = NS$)
	WOMAC total	Glucosamine preparation	5	Standardised mean difference (fixed-effects model): -0.15 (95% CI -0.30 to 0.00, $p = NS$)
	WOMAC total	Glucosamine preparation	2 Rotta, 3 non-Rotta	Standardised mean difference (fixed-effects model): Rotta -0.23 (95% CI -0.42 to -0.03, $p = 0.02$); non-Rotta -0.02 (95% CI -0.27 to 0.22, $p = NS$)

Study	Outcome	Factor	n	Results
	Number of patients reporting adverse events	Allocation concealment adequate, glucosamine vs placebo	7	Relative risk (fixed-effects model): 0.97 (95% CI 0.88 to 1.08, $p = NS$)
	Number of withdrawals due to adverse events	Allocation concealment adequate, glucosamine vs placebo	7 (9)	Relative risk (fixed-effects model): 0.78 (95% CI 0.52 to 1.18, $p = NS$)
Chondroitin				
Reichenbach 2007 ⁶¹	Pain (combined measures, see above)	Year of publication	20	Benefit of chondroitin decreased by an effect size of 0.08 per year (95% CI 0.04 to 0.12), i.e. newer publications had smaller effects, $p = 0.001$
	Pain	Placebo control (yes/no)	17 yes, 3 no	No significant difference in effect size
	Pain	Patient blinding	12 adequate, 8 unclear or no	No significant difference in effect size
	Pain	Duration of follow-up (> 6 months vs ≤ 6 months)	11 > 6 months, 9 ≤ 6 months	No significant difference in effect size
	Pain	Funding by non-profit organisation	1 yes, 19 unclear or no	No significant difference in effect size
	Pain	Route of administration (oral, intramuscular)	Oral 18, intramuscular 2	No significant difference in effect size
	Pain	Concealment of allocation	2 adequate, 18 unclear	Effect size: -0.01 (95% CI -0.12 to 0.10) for adequate allocation concealment; -0.84 (95% CI -1.08 to -0.59) for inadequate allocation concealment; p for interaction 0.05
	Pain	Intention-to-treat (ITT) analysis	3 yes, 17 no or unclear	Effect size: -0.03 (95% CI -0.13 to 0.07) for ITT; -0.88 (95% CI -1.13 to -0.64) for no ITT or unclear; p for interaction 0.017
	Pain	Analgesic cointervention	5 similar, 15 less in experimental group or unclear	Effect size: -0.30 (95% CI -0.62 to 0.02) for similar analgesic co-intervention; -0.92 (95% CI -1.26 to -0.59) for less analgesic in experimental group or unclear; p for interaction 0.043
	Pain	> 200 patients randomised vs ≤ 200 patients randomised	5 > 200, 15 ≤ 200	Effect size: -0.26 (95% CI -0.56 to 0.04) for > 200; -0.93 (95% CI -1.22 to -0.65) for ≤ 200; p for interaction 0.022
	Pain	Univariable meta-regression: follow-up duration, maximum treatment duration, dosage of chondroitin		No significant effect
NS, not significant; VAS, visual analogue scale.				

Appendix 5

Results of RCTs fulfilling inclusion criteria

Intention-to-treat values are reported where possible; all results are from end of trial unless stated otherwise.

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
Glucosamine						
<i>Structure</i>						
Kawasaki 2008 ²³	Joint space width	I: 2.6 mm, SD 1.2 C: 3.1 mm, SD 1.0		I: 0.0 (95% CI -2.2 to 1.7) C: -0.3 (95% CI -1.8 to 1.6)	18 months	NS
Pavelká 2002 ⁷⁷	Minimum joint space width	I: 3.89 mm, SD 1.48 C: 3.63 mm, SD 1.57		I: +0.04 (95% CI -0.06 to 0.14) C: -0.19 (95% CI -0.29 to -0.09) Difference: 0.23 mm (95% CI 0.09 to 0.37)	3 years	0.001
	Severe joint space narrowing (> 0.5 mm)		I: n = 5 C: n = 14 NNT = 11		3 years	0.05
Reginster 2001 ⁷⁶	Mean joint space width	Total joint space width: I: 5.23 mm, SD 1.36 C: 5.39 mm, SD 1.29		Change from baseline: I: -0.06 mm (95% CI -0.22 to 0.09) C: -0.31 mm (95% CI -0.48 to -0.13) Difference: 0.24 mm (95% CI 0.01 to 0.48)	3 years	0.043
	Minimum joint space width	I: 3.82 mm, SD 1.32 C: 3.95 mm, SD 1.24		Change from baseline: I: -0.07 mm (95% CI -0.22 to 0.07) C: -0.40 mm (95% CI -0.56 to -0.24) Difference: 0.33 mm (95% CI 0.12 to 0.54)	3 years	0.003
Pain/function						
Kawasaki 2008 ²³	JOA total score (range 0-100)	I: 74.2, SD 13.3 C: 69.6, SD 14.4		I: +13.7 (95% CI -18.5 to 43) C: +16.3 (95% CI -4.8 to 39.8)	18 months	NS
	JOA gait (range 0-30)	I: 23.3, SD 5.5 C: 21.5, SD 6.6		I: +4.4 (95% CI 2.8 to 11) C: +6.3 (95% CI -3.6 to 20)	18 months	NS
	JOA stairs (range 0-25)	I: 14.7, SD 5.6 C: 11.9, SD 6.1		I: +5.5 (95% CI -8.2 to 20.3) C: +6.3 (95% CI -1.1 to 17.5)	18 months	NS

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
Pavelká 2002 ⁷⁷	JOA range of motion (range 0–35)	I: 29.4, SD 5.0 C: 29.5, SD 4.8		I: +1.4 (95% CI –5.5 to 5.5) C: +1.9 (95% CI –6.1 to 10)	18 months	NS
	JOA swelling (range 0–10)	I: 6.8, SD 2.7 C: 6.7, SD 3.3		I: +2.6 (95% CI –0.3 to 5) C: +1.9 (95% CI –5.0 to 10)	18 months	NS
	VAS pain (range 0–10)	I: 5.0, SD 2.0 C: 4.9, SD 1.8		I: –1.6 (95% CI –5.0 to 2.2) C: –1.7 (95% CI –5.5 to 2.5)	18 months	NS
	WOMAC total (range 0–96)	I: 31.5, SD 15.6 C: 28.7, SD 16.0		I: –14.9 (95% CI –45.5 to 6) C: –11.5 (95% CI –38.8 to 7.5)	18 months	NS
	WOMAC pain (range 0–20)	I: 7.2, SD 3.9 C: 6.5, SD 3.4		I: –3.6 (95% CI –14.1 to 3) C: –2.9 (95% CI –9.5 to 0.5)	18 months	NS
	WOMAC stiffness (range 0–8)	I: 3.4, SD 1.6 C: 2.7, SD 1.6		I: –1.5 (95% CI –5.1 to 1.0) C: –0.7 (95% CI –3 to 1.5)	18 months	NS
	WOMAC function (range 0–68)	I: 20.8, SD 11.0 C: 19.6, SD 11.5		I: –9.8 (95% CI –31.2 to 5.2) C: –7.5 (95% CI –27.2 to 7)	18 months	NS
	Lequesne index (points)	I: 8.95, SD 2.30 C: 8.94, SD 2.27		Change from baseline: I: –1.7 (95% CI –2.2 to –1.2) C: –0.82 (95% CI –1.1 to –0.51) Difference: 0.91 (95% CI 0.34 to 1.5)	3 years	0.002
	WOMAC total (points)	I: 30.70, SD 14.40 C: 30.48, SD 14.43		Change from baseline: I: –8.0 (95% CI –9.8 to –6.3) C: –4.9 (95% CI –6.5 to 3.2) Difference: 3.1 (95% CI 0.77 to 5.5)	3 years	0.01
	WOMAC pain (points)	I: 6.61, SD 3.45 C: 6.33, SD 3.13		Change from baseline: I: –2.0 (95% CI –2.4 to –1.5) C: –1.3 (95% CI –1.7 to 0.88) Difference: 0.7 (95% CI 0.06 to 1.3)	3 years	0.03

continued

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
Reginster 2001 ⁷⁶	WOMAC function (points)	I: 21.84, SD 10.67 C: 22.00, SD 11.03		Change from baseline: I: -5.8 (95% CI -7.1 to -4.4) C: -3.7 (95% CI -4.9 to -2.5) Difference: 2.1 (95% CI 0.28 to 3.9)	3 years	0.02
		I: 2.25, SD 1.47 C: 2.15, SD 1.44		Change from baseline: I: -0.31 (95% CI -0.55 to 0.07) C: +0.11 (95% CI -0.12 to 0.34) Difference: 0.42 (95% CI 0.09 to 0.75)	3 years	0.01
		I: 1030.2 mm, SD 473.8 C: 939.7 mm, SD 484.8		Change from baseline: I: -11.7% (95% CI -20.3 to -3.2) C: +9.8% (95% CI -6.2 to 25.8) Difference: 21.6% (95% CI 3.5 to 39.6)	3 years	0.020
Reginster 2002 (pooled study) ⁵²	WOMAC pain	I: 194.1 mm, SD 101.9 C: 172.2 mm, SD 104.5		Change from baseline: I: ~-36.7 mm, SE 8.3 C: ~-7.5 mm, SE 10.6 mm (estimated from graph)	3 years	0.047
		I: 740.1 mm, SD 364.2 C: 670.8 mm, SD 367.8		Change from baseline: I: ~-160 mm, SE 24.2 C: ~-65.5 mm, SE 31.5 (estimated from graph)	3 years	0.020
		I: 96.0 mm, SD 54.8 C: 96.7 mm, SD 54.6			3 years	No significant difference between groups (no data shown)
Joint replacement Reginster 2001/Pavelká 2002 (pooled study) ⁵²	Joint replacement [in 275 patients (of 340 patients with at least 12 months' treatment), n = 144 glucosamine, n = 131 placebo]		I: 9/144 (6.3%) C: 19/131 (14.5%) RR 0.43 (95% CI 0.20 to 0.92, p = 0.024)		Mean 5 years after trial termination (8 years from beginning of treatment)	

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
Adverse events Kawasaki 2008 ⁷³	Withdrawals due to adverse events		I: n = 1 C: n = 2		18 months	
Pavelka 2002 ⁷⁷			I: 8 drop-outs due to adverse effects; at least one adverse event 66%; gastrointestinal tract and liver 25%; musculoskeletal 30%; cardiovascular 23%; skin and appendages 10%; respiratory tract 17%; urinary tract 12%; metabolic and nutritional 7%; other 14% C: 10 drop-outs due to adverse effects; at least one adverse event 64%; gastrointestinal tract and liver 28%; musculoskeletal 22%; cardiovascular 20%; skin and appendages 15%; respiratory tract 7%; urinary tract 11%; metabolic and nutritional 6%; other 14%		3 years	No significant difference between groups; no significant difference in routine laboratory tests between groups

continued

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
Reginster 2001 ⁷⁶			<p>I: 18 drop-outs due to adverse effects; at least one adverse event 94%; abdominal pain 12%; dyspepsia 4%; diarrhoea 9%; increased BP 14%; decreased BP 2%; cardiac failure 4%; fatigue 9%; headache 6%; vertigo 7%; neuritis 4%; depressive mood 6%; allergic episode 4%</p> <p>C: 21 drop-outs due to adverse effects; at least one adverse event 93%; abdominal pain 17%; dyspepsia 8%; diarrhoea 10%; increased BP 14%; decreased BP 8%; cardiac failure 7%; fatigue 7%; headache 4%; vertigo 3%; neuritis 6%; depressive mood 4%; allergic episode 7%</p>		3 years	No significant difference between groups; no great abnormalities in laboratory tests in both groups; no change in glycaemic homeostasis
Chondroitin Structure						
Michel 2005 ¹⁰⁸	Minimum joint space width	I: 2.41, SD 0.14 C: 2.35, SD 0.14		<p>Change from baseline: I: +0.045, SD 0.48 (95% CI -0.03 to 0.12) C: -0.07, SD 0.56 (95% CI -0.16 to 0.02) Difference between groups: 0.12, SD 0.52 (95% CI 0.00 to 0.24)</p>	2 years	0.05

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
	Mean joint space width	I: 3.04, SD 0.14 C: 3.00, SD 0.15		Change from baseline: I: 0.0, SD 0.53 (95% CI -0.08 to 0.09) C: -0.14, SD 0.61 (95% CI -0.24 to -0.04) Difference between groups: 0.14, SD 0.57 (95% CI 0.01 to 0.27)	2 years	0.04
Uebelhart 1998 ¹⁴	Medial femorotibial joint minimum width	I: (n = 14) 0.34 cm, SD 0.10 C: (n = 12) 0.40 cm, SD 0.10	I: (n = 14) 0.35 cm, SD 0.10 C: (n = 12) 0.36 cm, SD 0.13		1 year	NS
	Medial femorotibial joint mean width	I: (n = 14) 0.44 cm, SD 0.11 C: (n = 12) 0.51 cm, SD 0.10	I: (n = 14) 0.44 cm, SD 0.10 C: (n = 12) 0.46 cm, SD 0.14		1 year	< 0.05
	Medial femorotibial joint surface area	I: (n = 14) 1.08 cm ² , SD 0.32 C: (n = 12) 1.29 cm ² , SD 0.28	I: (n = 14) 1.09 cm ² , SD 0.33 C: (n = 12) 1.17 cm ² , SD 0.36		1 year	NS
	Bone metabolism				1 year	Significant effect on bone metabolism found: osteocalcin, pyridinoline/creatinine, and deoxypyridinoline/creatinine significantly higher, and keratin sulphate significantly lower than in placebo group, p = 0.001
Uebelhart 2004 ¹¹⁶	Joint surface area	I: 68.0 mm ² , SD 27.2 C: 63.3 mm ² , SD 24.4	I: 67.8 mm ² , SD 26.9 C: 58.7 mm ² , SD 20.9	Change from baseline: I: -0.19 mm ² (95% CI -3.56 to 3.17) C: -4.55 mm ² (95% CI -8.61 to -0.49) Difference: 4.36 mm ² (95% CI -0.19 to 8.91)	1 year	NS

continued

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
	Minimum joint space width	I: 3.65 mm, SD 1.46 C: 3.54 mm, SD 1.39	I: 3.61 mm, SD 1.51 C: 3.23 mm, SD 1.27	Change from baseline: I: -0.04 mm (95% CI -0.23 to 0.14) C: -0.32 mm (95% CI -0.57 to -0.07) Difference: 0.27 mm (95% CI 0.004 to 0.55)	1 year	0.047
	Mean joint space width	I: 4.20 mm, SD 1.51 C: 4.03 mm, SD 1.47	I: 4.20 mm, SD 1.58 C: 3.74 mm, SD 1.28	Change from baseline: I: -0.006 mm (95% CI -0.20 to 0.18) C: -0.29 mm (95% CI -0.53 to -0.04) Difference: 0.28 mm (95% CI 0.01 to 0.55)	1 year	0.039
<i>Pain/function</i>						
Michel 2005 ¹⁰⁸	WOMAC total	I: 2.3, SD 1.6 C: 2.6, SD 1.7		I: -3.9% C: +2.1%	2 years	NS
	WOMAC pain	I: 2.5, SD 1.6 C: 2.7, SD 1.8		I: -11.0% C: -6.2%	2 years	NS
	WOMAC function	I: 2.1, SD 1.6 C: 2.5, SD 1.8		I: -7.8% C: -4.6%	2 years	NS
	WOMAC stiffness	I: 3.0, SD 2.3 C: 3.5, SD 2.5		I: -0.8% C: +5.9%	2 years	NS
Uebelhart 1998 ¹¹⁴	Huskisson VAS (0-10 cm)	I: 5.76 cm, SD 1.61 C: 6.44 cm, SD 1.10	I: 2.1 cm, SD 2.1 C: 4.8 cm, SD 2.5		1 year	Between treatments $p < 0.001$, between times $p < 0.05$
	Overall mobility capacity (VAS)	I: 5.1 cm, SD 1.5 C: 5.7 cm, SD 1.6	I: 8.6 cm, SD 1.4 C: 6.8 cm, SD 2.3		1 year	Between treatments $p = NS$, between times $p < 0.001$
Uebelhart 2004 ¹¹⁶	Lequesne index	I: 9.0, SD 2.8 C: 9.1, SD 3.2	I: 5.8, SD 3.6 C: 7.0, SD 3.9	I: -36% C: -23%	1 year	<0.01

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
Adverse events Michel 2005 ¹⁰⁸	Huskisson VAS (0–100 mm)	I: 58.8 mm, SD 15.5 C: 61.1 mm, SD 19.0	I: 34.3 mm, SD 27.4 C: 45.8 mm, SD 27.6	I: -42% C: -25%	1 year	< 0.05
	Walking time	I: 24.5 seconds, SD 22.7 C: 22.8 seconds, SD 7.5	I: 20.1 seconds, SD 6.8 C: 22.7 seconds, SD 7.7	I: -18% C: -0.5%	1 year	< 0.05
Uebelhart 1998 ¹¹⁴	Clinical tolerance		I: 9 drop-outs due to adverse effects; upper respiratory tract infections 29%; headache 7%; abdominal pain 4%; allergic episode 6%; cardiac problem 6%; urinary tract infection 5% C: 9 drop-outs due to adverse effects; upper respiratory tract infections 31%; headache 9%; abdominal pain 11%; allergic episode 6%; cardiac problem 5%; urinary tract infection 5%		2 years	All differences NS
Uebelhart 2004 ¹¹⁶	Biological tolerability (blood, renal, liver biological parameters)		I: 2 drop-outs due to adverse events C: 1 drop-out due to adverse events		1 year	No details, stated that there was no significant difference in clinical side effects between the two groups No details, stated that there was no significant difference between the two groups No significant differences between groups, laboratory abnormalities only observed in placebo group

continued

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
Glucosamine/chondroitin						
<i>Structure</i>						
Rai 2004 ¹²⁰	Minimum joint space width	I: 3.66 mm C: 3.65 mm	I: 3.62 mm, $p = \text{NS}$ versus baseline C: 3.52 mm, $p \leq 0.01$ versus baseline		1 year	≤ 0.01
<i>Pain/function</i>						
Messier 2007 ¹²²	WOMAC pain	I: 7.1, SE 0.5 C: 5.9, SE 0.5	6 months: I: 6.2, SE 0.4 C: 6.2, SE 0.4 12 months: I: 6.0, SE 0.5 C: 5.18, SE 0.5		6 months and 1 year	NS
	WOMAC function	I: 25.9, SE 1.7 C: 21.1, SE 1.5	6 months: I: 21.9, SE 1.1 C: 22.9, SE 1.1 12 months: I: 19.4, SE 1.2 C: 20.6, SE 1.2		6 months and 1 year	NS
	6-minute walk	I: 384.7 m, SE 17.6 C: 398.7 m, SE 17.3	6 months: I: 393.6 m, SE 8.0 C: 396.5 m, SE 7.9 12 months: I: 409.2 m, SE 8.7 C: 410.5 m, SE 8.6		6 months and 1 year	NS
	Knee concentric extension strength	I: 209.4 N, SE 31.2 C: 163.9 N, SE 20.6	6 months: I: 176.9 N, SE 16.3 C: 202.7 N, SE 17.5 12 months: I: 207.6 N, SE 14.6 C: 209.7 N, SE 15.0		6 months and 1 year	NS

Study	Outcome	Baseline	End of study	Change from baseline/ difference between groups	Timing of outcome measure	p-value (between groups)
	Knee concentric flexion strength	I: 106.0 N, SE 16.1 C: 83.0 N, SE 10.9	6 months: I: 106.1 N, SE 7.3 C: 106.7 N, SE 7.8 12 months: I: 102.9 N, SE 7.7 C: 124.8 N, SE 8.3		6 months and 1 year	NS at 6 months, $p = 0.05$ at 12 months
	Balance (foot length)	I: 0.52, SE 0.04 C: 0.53, SE 0.03	6 months: I: 0.523, SE 0.014 C: 0.583, SE 0.017 12 months: I: 0.538, SE 0.017 C: 0.591, SE 0.020		6 months and 1 year	$p = 0.01$ at 6 months, $p = 0.05$ at 12 months
Rai 2004 ¹²⁰	Lequesne index	I: 4.6 C: 4.9	I: 3.7 C: 11.48		1 year	≤ 0.01
Adverse events Messier 2007 ¹²²	Adverse events		No details given but reported that the only adverse event was hair loss in one participant in the intervention group		1 year	

BP, blood pressure; C, control; N, Newton; NINT, number needed to treat; I, intervention; JOA, Japan Orthopaedic Association; NS, not significant; RR, relative risk; VAS, visual analogue scale.

Appendix 6

Results of RCTs fulfilling inclusion criteria – subgroups

Study	Subgroup	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value
Glucosamine Structure Reginster 2001 ⁷⁶ (Bruyere 2003 ²¹³)	Mean joint space width lowest quartile (< 4.5 mm, $n = 29$ intervention, $n = 23$ control) versus highest quartile (> 6.2 mm, $n = 27$ intervention, $n = 26$ control)	Change in mean joint space width			Joint space width < 4.5 mm: I: $+6.2\%$, SD 17.5; $+0.22$ mm, SD 0.66 C: $+3.8\%$, SD 23.8; $+0.13$ mm, SD 0.81 Joint space width > 6.2 mm: I: -6.0% , SD 15.1; -0.45 mm, SD 1.04 C: -14.9% , SD 17.9; -1.05 mm, SD 1.28	< 0.01 for joint space change between the two quartiles
Chondroitin Structure Michel 2005 ¹⁰⁸	Patients with minimum joint space width ≥ 1 mm at entry (I: $n = 114$, C: $n = 111$)	Minimum joint space width Mean joint space width			Change from baseline: I: $+0.05$, SD 0.53 (95% CI -0.05 to 0.14) C: -0.14 , SD 0.57 (95% CI -0.25 to -0.03) Difference: 0.19, SD 0.55 (95% CI 0.04 to 0.33) Change from baseline: I: $+0.01$, SD 0.54 (95% CI -0.09 to 0.11) C: -0.20 , SD 0.58 (95% CI -0.31 to -0.09) Difference: 0.21, SD 0.56 (95% CI 0.06 to 0.36)	0.01 0.006
						C, control; I, intervention.

Appendix 7

Health economics methods – informing the model

For developing the model of cost-effectiveness of glucosamine, information from the clinical review was used as the basis for evidence of the clinical effectiveness and QoL gains. A separate structured search was carried out to identify the evidence relating to the costs and health outcome measures that are used for economic evaluations of health-care interventions for knee OA.

A systematic review of literature was conducted to search for evidence on cost-effectiveness and cost of illness studies relating to OA and use of glucosamine and chondroitin. The MEDLINE and EMBASE medical literature databases were searched from 1950 to week 1 of February 2008 to identify relevant studies. We only considered studies in English.

The following search terms were used to find relevant cost-effectiveness studies: 'glucosamine'

and/or 'chondroitin', combined with 'economics', 'costs or economics', 'quality of life', 'quality adjusted life years', 'satisfaction'. This search retrieved 217 articles from MEDLINE(R), and we also ran those key words in EMBASE for the period 1980 to week 6 of 2008 and retrieved 180 papers. From the articles retrieved, the health economics research fellow read each abstract to identify whether the study was relevant for inclusion. A study was relevant if a comparison of costs and consequences (effectiveness, QoL or QALY) between placebo (or usual care) and glucosamine sulphate, glucosamine hydrochloride or chondroitin (or some combination of the three) was undertaken and reported in the paper. No relevant studies matched these criteria; thus, it was not possible to undertake a critical appraisal of published studies.



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