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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Executive summary

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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 Clinical Trials.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 Other sources included bibliographies of retrieved papers, registered but unpublished trials, internet searches and the Food Standards Agency website.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
At £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.

**Publication**

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series Health Technology Assessment.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

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.