

Glucosamine therapy for treating osteoarthritis (Review)

Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC,
Wells G



**THE COCHRANE
COLLABORATION[®]**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2008, Issue 4

<http://www.thecochranelibrary.com>



TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	3
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	4
METHODS OF THE REVIEW	4
DESCRIPTION OF STUDIES	5
METHODOLOGICAL QUALITY	6
RESULTS	6
DISCUSSION	9
AUTHORS' CONCLUSIONS	11
POTENTIAL CONFLICT OF INTEREST	12
ACKNOWLEDGEMENTS	12
SOURCES OF SUPPORT	12
REFERENCES	12
TABLES	16
Characteristics of included studies	16
Characteristics of excluded studies	29
ANALYSES	29
Comparison 01. Glucosamine versus placebo	29
Comparison 02. Glucosamine versus NSAIDs [Piroxicam, Ibuprofen]	30
Comparison 03. Glucosamine versus placebo (Allocation concealment A)	30
Comparison 04. Glucosamine versus placebo (Rotta preparation)	30
Comparison 05. Glucosamine versus placebo (non-Rotta preparation)	31
INDEX TERMS	31
COVER SHEET	31
GRAPHS AND OTHER TABLES	32
Analysis 01.01. Comparison 01 Glucosamine versus placebo, Outcome 01 Pain	32
Analysis 01.02. Comparison 01 Glucosamine versus placebo, Outcome 02 Lequesne Index	33
Analysis 01.03. Comparison 01 Glucosamine versus placebo, Outcome 03 Lequesne Index	34
Analysis 01.04. Comparison 01 Glucosamine versus placebo, Outcome 04 WOMAC Pain Subscale	34
Analysis 01.05. Comparison 01 Glucosamine versus placebo, Outcome 05 WOMAC Stiffness Subscale	35
Analysis 01.06. Comparison 01 Glucosamine versus placebo, Outcome 06 WOMAC Function Subscale	35
Analysis 01.07. Comparison 01 Glucosamine versus placebo, Outcome 07 WOMAC Total	36
Analysis 01.08. Comparison 01 Glucosamine versus placebo, Outcome 08 Mean Joint Space Width	36
Analysis 01.09. Comparison 01 Glucosamine versus placebo, Outcome 09 Minimum Joint Space Width	37
Analysis 01.10. Comparison 01 Glucosamine versus placebo, Outcome 10 Osteoarthritis Research Society International Responder Criteria (OARSI)	37
Analysis 01.11. Comparison 01 Glucosamine versus placebo, Outcome 11 Toxicity (Number of Patients Reporting Adverse Events)	38
Analysis 01.12. Comparison 01 Glucosamine versus placebo, Outcome 12 Toxicity (Number of Withdrawals due to Adverse Events)	39
Analysis 02.01. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 01 Pain	40
Analysis 02.02. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 02 Lequesne Index	40
Analysis 02.03. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 03 Toxicity (Number of Patients Reporting Adverse Events)	41
Analysis 02.04. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 04 Toxicity (Number of Withdrawals due to Adverse Events)	41
Analysis 03.01. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 01 Pain	42
Analysis 03.02. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 02 Lequesne Index	42

Analysis 03.03. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 03 Lequesne Index	43
Analysis 03.04. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 04 WOMAC Pain Subscale	43
Analysis 03.05. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 05 WOMAC Stiffness Subscale	44
Analysis 03.06. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 06 WOMAC Function Subscale	44
Analysis 03.07. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 07 WOMAC Total	45
Analysis 03.09. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 09 Minimum Joint Space Width	45
Analysis 03.11. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 11 Toxicity (Number of Patients Reporting Adverse Events)	46
Analysis 03.12. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 12 Toxicity (Number of Withdrawals due to Adverse Events)	46
Analysis 04.01. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 01 Pain	47
Analysis 04.02. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 02 Lequesne Index	48
Analysis 04.03. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 03 Lequesne Index	48
Analysis 04.04. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 04 WOMAC Pain Subscale	49
Analysis 04.05. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 05 WOMAC Stiffness Subscale	49
Analysis 04.06. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 06 WOMAC Function Subscale	50
Analysis 04.07. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 07 WOMAC Total	50
Analysis 05.01. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 01 Pain	51
Analysis 05.02. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 02 WOMAC Total	51
Analysis 05.04. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 04 WOMAC Pain Subscale	52
Analysis 05.05. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 05 WOMAC Stiffness Subscale	52
Analysis 05.06. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 06 WOMAC Function Subscale	53

Glucosamine therapy for treating osteoarthritis (Review)

Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G

This record should be cited as:

Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD002946. DOI: 10.1002/14651858.CD002946.pub2.

This version first published online: 20 April 2005 in Issue 2, 2005.

Date of most recent substantive amendment: 23 February 2005

ABSTRACT

Background

Osteoarthritis (OA) is the most common form of arthritis, and it is often associated with significant disability and an impaired quality of life.

Objectives

To review all randomized controlled trials (RCTs) evaluating the effectiveness and toxicity of glucosamine in OA.

Search strategy

We searched MEDLINE, PREMEDLINE, EMBASE, AMED, ACP Journal Club, DARE, CDSR, and CENTRAL. We also wrote letters to content experts, and hand searched reference lists of identified RCTs and pertinent review articles. All searches were updated in January 2005.

Selection criteria

Relevant studies met the following criteria: 1) RCTs evaluating the effectiveness and safety of glucosamine in OA, 2) Both placebo controlled and comparative studies were eligible, 3) Both single blinded and double blinded studies were eligible.

Data collection and analysis

Data abstraction was performed independently by two investigators and the results were compared for degree of agreement. Gotzsche's method and a validated tool (Jadad 1996) were used to score the quality of the RCTs. Continuous outcome measures were pooled using standardized mean differences (SMD) as the measure of effect size. Dichotomous outcome measures were pooled using relative risk ratios (RR).

Main results

Analysis restricted to eight studies with adequate allocation concealment failed to show benefit of glucosamine for pain and WOMAC function. Collectively, the 20 analyzed RCTs favoured glucosamine with a 28% (change from baseline) improvement in pain (SMD -0.61, 95% CI -0.95, -0.28) and a 21% (change from baseline) improvement in function using the Lequesne index (SMD -0.51 95% CI -0.96, -0.05). However, the results are not uniformly positive, and the reasons for this remain unexplained. WOMAC pain, function and stiffness outcomes did not reach statistical significance.

In the 10 RCTs in which the Rotta preparation of glucosamine was compared to placebo, glucosamine was found to be superior for pain (SMD -1.31, 95% CI -1.99, -0.64) and function using the Lequesne index (SMD -0.51, 95% CI -0.96, -0.05). Pooled results for pain (SMD -0.15, 95% CI -0.35, 0.05) and function using the WOMAC index (SMD 0.03, 95% CI -0.18, 0.25) in those RCTs in which a non-Rotta preparation of glucosamine was compared to placebo did not reach statistical significance. In the four RCTs in which the Rotta preparation of glucosamine was compared to an NSAID, glucosamine was superior in two, and equivalent in two. Two RCTs using the Rotta preparation showed that glucosamine was able to slow radiological progression of OA of the knee over a three year period (SMD 0.24, 95% CI 0.04, 0.43).

Glucosamine was as safe as placebo in terms of the number of subjects reporting adverse reactions (RR=0.97, 95% CI, 0.88, 1.08).

Authors' conclusions

This update includes 20 studies with 2570 patients. Pooled results from studies using a non-Rotta preparation or adequate allocation concealment failed to show benefit in pain and WOMAC function while those studies evaluating the Rotta preparation show that glucosamine was superior to placebo in the treatment of pain and functional impairment resulting from symptomatic OA. 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. Glucosamine was as safe as placebo.

PLAIN LANGUAGE SUMMARY

Glucosamine for osteoarthritis

Does glucosamine work for treating osteoarthritis?

This Cochrane review looked at the best studies done to date on glucosamine. Twenty studies tested over 2500 people with osteoarthritis of the knee or hip. Most of the studies were 2 to 3 months long. To test how well glucosamine works, researchers compared people who had either glucosamine (as a pill or an injection), fake pills or injections, or a non-steroidal anti-inflammatory drug (NSAID).

What is osteoarthritis and glucosamine?

Osteoarthritis (OA) is the most common form of arthritis that can affect the hands, hips, shoulders and knees. In OA, the cartilage that protects the ends of the bones breaks down and causes pain and swelling. Drug and non-drug treatments are used to relieve pain and/or swelling. Glucosamine can be found naturally in the body and is one of the building blocks of cartilage. It is thought that taking glucosamine supplements may help stop cartilage breakdown, build cartilage and decrease swelling. But there is debate about its effects.

How well does glucosamine work?

Pain: The high quality studies showed that pain improved about the same whether people took glucosamine or fake pills. If all of the studies are examined (including low quality and old studies), then glucosamine improved pain more than fake pills.

- Pain may improve by 13 more points on a scale of 0 to 100 with glucosamine than with fake pills.

Studies testing only the Rotta brand of glucosamine (including low quality and old studies) showed that glucosamine improved pain more than fake pills.

Function: The high quality studies show that glucosamine improved pain more than fake pills when measured by one type of scale, but improved the same amount as fake pills when measured by another scale. This result is the same whether all of the studies (including low quality and old studies) or whether studies using the Rotta brand of glucosamine are analysed.

How safe is it?

The number of people taking glucosamine who had side effects was about the same as the number who took fake pills. Side effects mainly included stomach upset and other joint pain.

What is the bottom line?

It was shown in a previous Cochrane review that glucosamine taken for 6 weeks decreases pain and improves function (physical ability) in people with osteoarthritis.

When compared to the previous review, this review which analyzes newer studies and more high quality studies, shows there is "platinum" level evidence that pain does not improve as much when taking glucosamine for 2 to 3 months. Depending on the scale used to measure function (physical ability), function may not improve at all or as much.

Glucosamine seems to be safe.

BACKGROUND

Osteoarthritis (OA) is the most common form of arthritis, and it is often associated with significant disability and an impaired quality of life (Badley 1995; Moralestorres 1996; Scott 1993; Towheed 1998). An estimated 12.1% of Americans age 25 and older (nearly 21 million persons in 1990) have clinical signs and symptoms of OA (Lawrence 1998). Among US adults age 30 years or older, symptomatic disease in the knee occurs in approximately 6% and symptomatic disease in the hip occurs in approximately 3% (Felson 2000). OA of the hip and knee can be especially disabling to lower extremity functioning because the hip and knee are large weight-bearing joints (Liang 1984). Advanced OA of the hip and knee is the most common reason for elective joint replacement (Hochberg 1996).

Although there are no curative therapies currently available for OA, individualized treatment programs are available to help relieve pain and stiffness, and to maintain and/or improve functional status (ACR 2000; Creamer 1998; Hochberg 1995a; Hochberg 1995b). Treatment strategies for OA have included both non-pharmacological and pharmacological modalities (Creamer 1997). Non-pharmacological therapy is considered to be a foundation for the successful medical management of OA (Felson 1998; Puett 1994). These modalities include weight reduction (if obese), physiotherapy (eg. muscle strengthening), and occupational therapy (eg. use of assistive devices for ambulation).

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered by many physicians to be the preferred agents for the pharmacological management of OA. In support of this, randomized controlled trials (RCTs) attest to the superior efficacy of NSAIDs as compared with placebo (Towheed 1997a; Towheed 1997b; Towheed 2002). However, there are certain disadvantages of routinely using NSAIDs in OA. For example, all NSAIDs (non-selective and COX-2 selective) are associated with significant potential toxicity, particularly in the elderly population (Devriere 2002; Gabriel 1991; Garner 2002; Griffin 1991; Wright 2002). COX-2 selective inhibitors have also been associated with an increased risk for cardiovascular disease. Rofecoxib, a COX-2 selective inhibitor, was recently withdrawn from the world market due to concerns in this regard (Sibbald 2004).

There is also a concern that NSAIDs may be toxic to articular cartilage (Herman 1986), and that they may accelerate the course of OA of the hip (Rashad 1989). Given that OA is the most prevalent form of arthritis and that the number of persons affected with OA will increase significantly in the near future, finding alternative, safer pharmacological therapies for OA is of considerable importance.

Recent additions to the options for pharmacological therapy of OA have included biological compounds, such as hyaluronans, chondroitin sulfate and glucosamine (Lozada 1997). Although not yet proven, these compounds may also potentially be chon-

droprotective, in that they may favourably modify the natural progression and course of OA. Glucosamine compounds, in particular, have attracted a great deal of attention, mostly in the lay press, and lesser so in the scientific literature (Anderson 2005; Barclay 1998; Da Camara 1998; Towheed 1999; Towheed 2000; Towheed 2002; Towheed 2003). There appears to be controversy as to the relative efficacy of glucosamine, and as to whether glucosamine can indeed modify the progression of OA (Register 2003).

For the purposes of this review, GS refers to glucosamine sulfate and GH refers to glucosamine hydrochloride, whereas glucosamine refers to both compounds. GS is a natural substance, and is the building block of the ground substance of the articular cartilage, the proteoglycans. The rationale for the use of GS in OA is based largely on in-vitro and animal models of osteoarthritis. For example, GS has been shown to normalize cartilage metabolism, rebuild experimentally damaged cartilage, and demonstrate mild anti-inflammatory properties (Bassleer 1992; McCarty 1994, Roden 1956; Rovati 1993; Setnikar 1991; Vidal 1978).

OBJECTIVES

To assess the effectiveness and toxicity of glucosamine in the pharmacological management of OA. Both symptomatic effectiveness and structural effectiveness (i.e.. delay in radiological progression of OA) will be evaluated.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Two levels of criteria were used to identify all relevant studies for this review. The first criteria was used to screen all citations that involve glucosamine in the management of OA. The second criteria were used to identify those studies that meet the following additional requirements: 1) RCTs evaluating the efficacy and toxicity of glucosamine in OA, 2) Both placebo-based and/or comparative studies were eligible, 3) Both single blinded and double blinded trials were eligible, 4) Studies to be included in the quantitative portion of the review (meta-analysis) must have presented suitable quantitative data for pooling across trials, 5) Studies that enrolled subjects with OA at any site were eligible, with the only exception being studies that evaluated glucosamine in temporomandibular joint (TMJ) disorders, 6) Only studies which evaluated glucosamine only preparations were included. Studies which evaluated combination products containing glucosamine in association with other active compounds (eg. chondroitin) were excluded, 7) Glucosamine could have been administered by any route.

Types of participants

All adult (age 18 years and older) humans with a diagnosis of either primary or secondary OA at any site, including the axial and peripheral skeleton. Studies that evaluated glucosamine in disorders of the temporomandibular joint (TMJ) were excluded from this review.

Types of intervention

Only studies that evaluated the efficacy and/or toxicity of glucosamine in OA were eligible. Both placebo-based and comparative RCTs were included.

Types of outcome measures

At least one outcome measure must have been used to measure response to treatment. The main outcome measures of pain, range of motion, functional assessments, and global assessments, would satisfy this criterion. The hierarchy of outcomes that were extracted consisted of (Bellamy 1997): 1) Pain measured by any method, 2) Functional assessment measured by a validated health status questionnaire (for example, the WOMAC), 3) Patient global assessment, 4) Physician global assessment, and 5) Range of motion of study joint. Structural benefits, defined as the ability of glucosamine to delay the natural radiological progression of OA, were also studied. Toxicity of glucosamine was also considered to represent a relevant outcome measure (measured by the number of subjects reporting any adverse events and by the number of withdrawals due to toxicity).

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Musculoskeletal Group methods used in reviews.

A MEDLINE search including the years 1966 to November 1999 (inclusive) was used to identify all relevant RCTs for the first version of this Cochrane Review. For the second version of this Cochrane Review, all searches were updated in January 2005. The same MEDLINE search strategy was extended for this version of the review to include the time period 1999 to November Week 3 2004. MEDLINE In-Process and other non-indexed citations were also searched as of January 2005. MEDLINE Daily Update was searched in January 2005. In addition, the Cochrane Controlled Trials Register (CCTR), the Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club and Database of Abstracts of Reviews of Effectiveness (DARE) was searched up to October 2004. Allied and Complementary Medicine (AMED) was searched for the time period of 1985 to January 2005. EMBASE was searched for the time period 1980 to 2005 week 2. No language or age restrictions were used for any of the electronic searches. Reference lists of all identified citations were manually searched. In addition, letters were sent to authors and content experts for assistance in retrieving additional RCTs,

especially those that were unpublished. A major manufacturer of glucosamine (Rotta Pharm) was also contacted for additional trials.

Search Strategy in MEDLINE, EMBASE, CCTR/CDSR/ACP Journal Club/DARE and AMED (All searches were run in January 2005):

1. exp osteoarthritis/
2. (degenerative adj2 arthritis). tw.
3. osteoarthr\$.tw.
4. or/1-3
5. exp glucosamine/
6. glucosamine.rn, tw.
7. acetylglucosamine.tw, rn.
8. n-acetylglucosamine.tw.
9. n-acetyl-d-glucosamine.tw.
10. or/5-9
11. 4 and 10
12. limit 11 to human

METHODS OF THE REVIEW

Study identification (identifying citations that involve GS/GH in the therapy of OA). Two investigators (TT and TP) used the screening criteria to review all identified citations independently. All citations identified by either investigator were retrieved and analyzed for suitability. Authors of abstracts were contacted requesting the full manuscript, including the raw and final data incorporating the results.

Study Selection (screening identified citations to see if they meet our additional criteria). Two investigators (TT and TP) reviewed each relevant citation independently to see if it met the selection criteria described previously. At this stage, an emphasis was placed on selecting RCTs, and excluding non-randomized treatment studies. If the randomization status was not clear, the article was withheld, pending clarification from the principal author. In situations where authors were not available, then a consensus was reached amongst the investigators.

Data Extraction

Two investigators (TT and TP) independently reviewed each RCT and extracted the raw data (for example, trial characteristics, subject demographics, outcome variables, results, features of trial quality, etc) by using a standardized form. If outcome data were not reported in a form suitable for quantitative pooling in a meta-analysis, the primary author was contacted for access to this information. Data on adverse effects were also extracted from the RCTs. A consensus method was used in the event of disagreement.

Data Analysis

For quantitative outcome data, standardized mean differences (SMD) were used to pool across RCTs (Hedges 1985; Pettiti

1994). It is important to note that we used the end of study means and standard deviations for the meta-analyses. If either of these were not available in the trial report, the principal author was contacted for additional information. In the absence of this information, we estimated the end of study standard deviation by using the baseline standard deviation. For categorical outcome data with two categories, the Relative Risk ratio (RR) was calculated (Petitti 1994). Heterogeneity was tested with a chi square test. Fixed effects models were used unless heterogeneity was significant ($p < 0.10$), in which case the random effects models were used. For the qualitative review of the studies, Gotzsche's method (Gotsche 1989) was used to score the quality of the RCTs. This method has been used by us previously to score the quality of RCTs in OA of the hip and knee, and also by Gotzsche to score the quality of NSAID trials in rheumatoid arthritis (RA) (Gotsche 1989; Towheed 1997a; Towheed 1997b). By using the same methodology to evaluate the quality of a trial, results obtained from the glucosamine trials are directly comparable to results obtained from the NSAID trials in both OA of the hip and knee, as well as from NSAID trials in RA. A second method was also used to score the methodological quality of the RCTs (Jadad 1996). The adequacy of allocation concealment was also recorded for each RCT (Schulz 1995).

Sensitivity and Subgroup Analysis

An ad-hoc sensitivity analysis was carried out to see if effect sizes varied on pain, function and radiologic measures when only those studies with adequate allocation concealment (score of 'A') were analyzed. An ad-hoc subgroup analysis was performed on those studies using the Rotta preparation of glucosamine versus those that did not use the Rotta preparation to determine if effect sizes varied on pain and function.

DESCRIPTION OF STUDIES

Results of Search Strategy:

The MEDLINE search strategy (1966 to November 1999, inclusive) resulted in a total of 61 citations. From these 61 citations, eleven RCTs were identified that evaluated the efficacy of glucosamine (Crolle 1980; D'ambrosio 1981; Drovanti 1980; Houpt 1999; Muller-FassBender 94; Noack 1994; Pujalte 1980; Qiu 1998; Reichelt 1994; Vaz 1982; Vajradul 1981). The updated MEDLINE search from 1996 to November Week 3 2004 resulted in a total of 201 citations. An additional four RCTs were identified from this search (Hughes 2002; Pavelka 2002; Reginster 2001; Rindone 2000). The EMBASE search from 1980 to 2003 Week 28 resulted in a total of 207 citations, of which one additional RCT was identified (Zenk 2002). Another EMBASE search from 1996 to 2005 Week 02 resulted in a total of 280 references of which one additional RCT was identified (Usha 2004). The MEDLINE in-Process and other Non-Indexed citations search as of January 6, 2005 resulted in 8 citations containing two addi-

tional RCTs (Cibere 2004; McAlindon 2004). MEDLINE daily update as of November 17, 2004 did not identify any relevant citations. The CDSR, ACP Journal Club, DARE and CCTR search as of October 2004 identified a total of 52 citations, but no additional RCTs were found. AMED identified 24 citations, but no additional RCTs were found. One unpublished full manuscript reporting a RCT was sent to us by Rotta Pharm; a reference to this study is available in abstract form (Rovati 1997). This study was included in the meta-analysis since the full manuscript contained all the relevant details necessary for its critical appraisal and for inclusion in the quantitative portion of the review. Rotta Pharm also sent us three unpublished brief technical reports reporting RCTs evaluating their GS preparation. These three brief unpublished technical reports were not included in the meta-analyses. No additional RCTs were identified by contact with content experts. Therefore, collectively the search strategies resulted in a total of 20 English language RCTs (19 published and 1 unpublished) that were included in the meta-analysis.

Trial Demographics and Features:

The 20 identified RCTs that were included in the meta-analysis are listed in the included characteristics Table. The years of publication (or reporting date) range from 1980 to 2004. Six RCTs were published in the 1980s, six were published (or reported) in the 1990s, and eight were published in the years 2000 to 2004. All are double-blind randomized parallel-group trials and contain a total of 2596 adult subjects with a mean age of 61.1 years (67% were female). A total of 1182 subjects were randomized to treatment with glucosamine and 1414 were randomized to the comparator groups (placebo or active comparator). The mean number of subjects randomized in the 20 RCTs was 129 (59 to glucosamine groups and 70 to comparator groups). The mean number completing the RCTs was 111 (86% completed the RCTs). The mean trial duration was 23.7 weeks. Excluding the two three year RCTs (Reginster 2001 and Pavelka 2002) resulted in a mean trial duration of 9 weeks. The country of origin (number of RCTs) included Italy (3), Germany (3), Canada (2), France (1), Thailand (1), China (1), Portugal (1), USA (3), UK (1), Philippines (1), Belgium (1), India (1) and the Czech Republic (1). Only five North American RCTs were found (Cibere 2004; Houpt 1999, McAlindon 2004; Rindone 2000; Zenk 2002). Seventeen of the 20 RCTs compared glucosamine to placebo (16 used GS and one used GH), whereas, four RCTs compared GS to an NSAID (ibuprofen in three and piroxicam in one). One study compared GS to both an NSAID and to placebo (Rovati 1997). The method of administration of glucosamine was quite variable in the RCTs. Sixteen used exclusively an oral route, two used an intra-articular (IA) route, three used an intra-muscular (IM) route, one used an intra-venous (IV) route, and two used multiple routes (IM or IA and IM or intra-venous (IV)). The dosage of glucosamine used in the RCTs was also quite variable. In the 16 RCTs using an oral route, the dosage was 1500 mg/day, which was administered as either 1500 mg once daily (4 RCTs) or as 500 mg three times per day (12 RCTs). In

the RCTs using parenteral routes (IM, IA, IV), 400 mg of GS was administered either once on a daily basis (2 RCTs) or twice weekly (1 RCT).

The type and site of OA evaluated was also heterogeneous in the 20 RCTs. Sixteen RCTs evaluated the knee exclusively, two evaluated OA at multiple sites (knee, hip, others), and two did not specify the location of OA that was being evaluated. Subjects with only primary OA were evaluated by seven RCTs; 13 RCTs did not make clear the distinction between primary and secondary OA. The method of classification of OA was not described in eleven RCTs, whereas, five used the Lequesne's Index, six used the American College of Rheumatology (ACR) classification criteria and two RCTs used both the ACR and Lequesne classification criteria. Radiographs of the target joints were obtained at baseline in 14 of the RCTs. Ten of these RCTs used published validated x-ray classification criteria for OA.

The outcome variables (number of RCTs) included pain (20), range of motion (6), functional status (15), global patient derived (1), global investigator derived (9), radiographic assessment for changes in cartilage thickness (2), and health related quality of life (0). Seven RCTs used the WOMAC instrument. Six RCTs used the Lequesne Index.

A majority of the RCTs (13/20 or 65%) had some form of relationship (evaluated the Rotta brand of GS and/or had some other affiliation) with Rotta Pharm, an Italian pharmaceutical manufacturer of GS. Six RCTs did not use the Rotta brand of glucosamine (Cibere 2004; Houpt 1999; Rindone 2000; Hughes 2002; Zenk 2002 and Usha 2004). One RCT used both a non-Rotta glucosamine preparation (about 90% of subjects received this) and a Rotta glucosamine preparation (about 10% of subjects received this) (McAlindon 2004). Thirteen of the RCTs (65%) only evaluated the Rotta brand of GS.

The four identified RCTs that were not included in the meta-analysis are listed in the excluded characteristics Table (Braham 2003, Magi 1997, Pipitone 1997, Rovati 1993). Reasons for their exclusion are also outlined in the Table.

METHODOLOGICAL QUALITY

The scoring checklist designed by Gotzsche 1989 for NSAID trials in RA and another validated scale (Jadad 1996) were used to score the methodological quality of the 20 glucosamine RCTs that were included in the meta-analysis. For the Gotzsche checklist, both the design and analysis scores were calculated for each of the RCTs. Both the design and analysis scores are rated from 0 to 8, with a higher score indicating higher quality. The four excluded RCTs were not scored. The median design and analysis scores in the 20 RCTs were 4 (out of 8) and 7 (out of 8). The mean design and analysis scores in the 20 RCTs were 3.7 and 6.3, respectively. The median and mean total scores were 10 and 10 (out of 16),

respectively. It is interesting to note that there was an overall strong trend for improvement in the quality scores over time encompassing the three decades in which these RCTs were conducted. RCTs published in the 1990s were much stronger than RCTs published in the 1980s (median design and analysis scores of 5 and 7, versus 2 and 6.5, respectively). RCTs published in the year 2000 or later were similar in quality to those published in the 1990s, with median design and analysis scores of 5 and 6.5.

Methodological quality was also assessed using a validated tool (Jadad 1996). The components of quality are the quality of randomization, quality of double blinding and reporting of withdrawals. The Jadad quality scoring system is scored from 0 to 5, with a higher score reflective of higher quality. For the 20 included RCTs, the median and mean scores were 4 and 4.2, respectively. RCTs that were published in the 1980s had a median Jadad score of 3, whereas, RCTs published in the 1990s and 2000s had median Jadad scores of 4.5 and 4.5, respectively.

The quality of the glucosamine RCTs was compared to NSAID trials in OA of the hip and knee, when using the similar scoring checklist (Gotsche 1989). In comparison with NSAID trials in OA of the hip and knee, the glucosamine trials were superior in the median design scores (4 versus 2 out of 8), and also superior in the median analysis scores (7 versus 4 and 5 out of 8, respectively). It can be appreciated that glucosamine trials were collectively as good (if not better) than NSAID trials in OA (Towheed 1997a, Towheed 1997b, Towheed 2003). Gotzsche 1989 applied his checklist to NSAID trials in RA and calculated a median design score of two and a median analysis score of three (each out of 8).

There were specific weaknesses with these RCTs. For example, there was a general lack of standardization of the OA diagnosis and a lack of standardization of outcome assessment. This weakness has been associated with most of the previously published trials of pharmacological therapy in OA (Towheed 1997a, Towheed 1997b). The methods used for ensuring blinding of subjects and investigators, as well as of randomising subjects to treatment groups were usually not provided. Only ten RCTs (50%) were rated as having adequate allocation concealment, whereas ten RCTs (50%) were rated as having inadequate allocation concealment. In the table of included studies, a score of A means that allocation concealment was adequately described in the RCT. A score of C means an unclear and/or inadequate allocation concealment status. Many of these specific weaknesses have been significantly addressed and improved upon in the more recently published RCTs.

RESULTS

1. Comparing GS or GH versus placebo: Results from 15 RCTs were pooled for the outcome variable of reduction in pain-where pain was measured by a number of different methods (Cibere 2004; Crolle 1980; D'ambrosio 1981; Drovanti 1980, Houpt

1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Pujalte 1980; Reginster 2001; Rindone 2000; Rovati 1997; Usha 2004; Vajradul 1981; Zenk 2002). The summary SMD (random effects) was -0.61 (95% CI, -0.95 to -0.28). A negative SMD in this case means that glucosamine was significantly superior to placebo in terms of its ability to reduce levels of pain.

2. Comparing GS to placebo for the Lequesne Index scores: Results from four RCTs were pooled (Noack 1994; Pavelka 2002; Reichelt 1994, Rovati 1997). The summary SMD (random effects) was -0.51 (95% CI, -0.96 to -0.05). A negative SMD in this case means that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne Index scores.

3. Comparing GS to placebo for Lequesne Index scores in which the outcome was dichotomous (% responders based on change in Lequesne Index): Relative risk ratios (RR) were pooled across two RCTs (Noack 1994; Reichelt 1994). The summary RR (fixed effects) for likelihood of being a responder was 1.52 (95% CI, 1.20 to 1.91).

4. Comparing GS or GH to placebo for WOMAC pain subscale scores: The summary SMD (fixed effects) for seven RCTs (Cibere 2004; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Zenk 2002) was -0.04 (95% CI, -0.17 to 0.09). In this outcome, there was no statistical difference between glucosamine and placebo.

5. Comparing GS or GH to placebo for WOMAC stiffness subscale scores: The summary SMD (fixed effects) for five RCTs (Cibere 2004; Houpt 1999; Hughes 2002; Pavelka 2002; Zenk 2002) was -0.06 (95% CI, -0.23 to 0.11). In this outcome, there was no statistical difference between glucosamine and placebo.

6. Comparing GS or GH to placebo for WOMAC function subscale scores: The summary SMD (fixed effects) for six RCTs (Cibere 2004; Houpt 1999; Hughes 2002; Pavelka 2002; Reginster 2001; Zenk 2002) was -0.07 (95% CI, -0.21 to 0.08). In this outcome, there was no statistical difference between glucosamine and placebo.

7. Comparing GS or GH to placebo for WOMAC total scores: The summary SMD (fixed effects) for five RCTs (Cibere 2004; Houpt 1999; Pavelka 2002; Reginster 2001; Zenk 2002) was -0.15 (95% CI, -0.30 to 0.00). In this outcome, there was no statistical difference between glucosamine and placebo.

8. Comparing GS to placebo for changes in minimum joint space width for the knee: The summary SMD (fixed effects) for two RCTs (Pavelka 2002; Reginster 2001) was 0.24 (95% CI, 0.04 to 0.43). This is statistically significant in favour of glucosamine and shows that glucosamine slows the natural radiological progression of OA of the knee over a three year period.

9. Comparing GS to an NSAID (piroxicam, ibuprofen) for the outcome variable of pain-where pain was measured by a number of different methods: The summary pooled SMD (fixed effects) for

three RCTs was -0.40 (95% CI, -0.60 to -0.19) (Qiu 1998; Rovati 1997; Vaz 1982). A negative SMD in this case means that glucosamine was significantly superior to NSAID in terms of its ability to improve pain.

10. Comparing GS to an NSAID (piroxicam, ibuprofen) for the outcome variable of change in the Lequesne Index scores: The summary SMD (random effects) for two pooled studies was -0.36 (95% CI, -1.07 to 0.35) (Muller-FassBender 94; Rovati 1997). In this outcome, there was no statistical difference between glucosamine and placebo.

Sensitivity Analysis:

Adequate allocation concealment:

11. Comparing GS or GH versus placebo in studies with adequate allocation concealment: Results from eight RCTs were pooled for the outcome variable of reduction in pain-where pain was measured by a number of different methods (Cibere 2004; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Rovati 1997; Zenk 2002) (The summary SMD (random effects) was -0.19 (95% CI, -0.50 to 0.11). In this outcome, there was no statistical difference between glucosamine and placebo.

12. Comparing GS to placebo in studies with adequate allocation concealment for the Lequesne Index scores: Results from three RCTs were pooled (Noack 1994, Rovati 1997, Pavelka 2002). The summary SMD (random effects) was -0.61 (95% CI, -1.21 to -0.01). A negative SMD in this case means that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne Index scores.

13. Comparing GS to placebo in studies with adequate allocation concealment for Lequesne Index scores in which the outcome was dichotomous (% responders based on change in Lequesne Index): The summary RR (fixed effects) from one RCT (Noack 1994) for likelihood of being a responder was 1.43 (95% CI, 1.08 to 1.91).

14. Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC pain subscale scores: The summary SMD (fixed effects) for seven RCTs (Cibere 2004; Houpt 1999; Hughes 2002; McAlindon 2004; Pavelka 2002; Reginster 2001; Zenk 2002) was -0.04 (95% CI, -0.17 to 0.09). In this outcome, there was no statistical difference between glucosamine and placebo.

15. Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC stiffness subscale scores: The summary SMD (fixed effects) for five RCTs (Cibere 2004; Houpt 1999; Hughes 2002; Pavelka 2002; Zenk 2002) was -0.06 (95% CI, -0.23 to 0.11). In this outcome, there was no statistical difference between glucosamine and placebo.

16. Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC function subscale scores: The summary SMD (fixed effects) for six RCTs (Cibere 2004; Houpt 1999; Hughes 2002; Pavelka 2002; Reginster 2001; Zenk 2002)

was -0.07 (95% CI, -0.21 to 0.08). In this outcome, there was no statistical difference between glucosamine and placebo.

17. Comparing GS or GH to placebo in studies with adequate allocation concealment for WOMAC total scores: The summary SMD (fixed effects) for five RCTs (Cibere 2004; Houpt 1999; Pavelka 2002; Reginster 2001; Zenk 2002) was -0.15 (95% CI, -0.30 to 0.00). In this outcome, there was no statistical difference between glucosamine and placebo.

18. Comparing GS to placebo in studies with adequate allocation concealment for changes in minimum joint space width for the knee: The summary SMD (fixed effects) for two RCTs (Reginster 2001, Pavelka 2002) was 0.24 (95% CI, 0.04 to 0.43). This is statistically significant in favour of glucosamine and shows that glucosamine slows the natural radiological progression of OA of the knee over a three year period.

Subgroup Analysis

Rotta preparation

19. Comparing GS to placebo in studies using the Rotta preparation for pain: Results from seven RCTs were pooled (Crolle 1980; D'ambrosio 1981; Drovanti 1980; Pavelka 2002; Pujalte 1980; Reginster 2001; Rovati 1997) for the outcome variable of reduction in pain. The summary SMD (random effects) was -1.31 (95% CI, -1.99, -0.64). A negative SMD in this case means that glucosamine was significantly superior to placebo in terms of its ability to reduce pain.

20. Comparing GS to placebo in studies using the Rotta preparation for the Lequesne Index scores: Results from four RCTs were pooled (Noack 1994; Pavelka 2002; Reichelt 1994; Rovati 1997). The summary SMD (random effects) was -0.51 (95% CI, -0.96 to -0.05). A negative SMD in this case means that glucosamine was significantly superior to placebo in terms of its ability to improve Lequesne Index scores.

21. Comparing GS to placebo in studies using the Rotta preparation for Lequesne Index scores in which the outcome was dichotomous (% responders based on change in Lequesne Index): The summary RR (fixed effects) from two RCT (Noack 1994; Reichelt 1994) for likelihood of being a responder was 1.52 (95% CI, 1.20 to 1.91).

22. Comparing GS to placebo in studies using the Rotta preparation for WOMAC pain subscale scores: Results from two RCTs were pooled (Pavelka 2002; Reginster 2001). The summary SMD (fixed effects) was -0.10 (95% CI, -0.29, 0.09). In this outcome, there was no statistical difference between glucosamine and placebo.

23. Comparing GS to placebo in studies using the Rotta preparation for WOMAC stiffness subscale scores: Result from one RCT (Pavelka 2002) was -0.22 (95% CI, -0.50, 0.06). In this outcome, there was no statistical difference between glucosamine and placebo.

24. Comparing GS to placebo in studies using the Rotta preparation for WOMAC function subscale scores: Results from two RCTs were pooled (Pavelka 2002; Reginster 2001). The summary SMD (fixed effects) was -0.14 (95% CI, -0.34, 0.05). In this outcome, there was no statistical difference between glucosamine and placebo.

25. Comparing GS to placebo using the Rotta preparation for WOMAC total scores: The summary SMD (fixed effects) for two RCTs (Pavelka 2002; Reginster 2001) was -0.23 (95% CI, -0.42 to -0.03). A negative SMD in this case means that glucosamine was statistically significantly superior to placebo.

Non-Rotta preparation

26. Comparing GS to placebo in studies using a non-Rotta preparation for pain: Results from eight RCTs were pooled (Cibere 2004; Houpt 1999; Hughes 2002; McAlindon 2004; Rindone 2000; Usha 2004; Vajaradul 1981; Zenk 2002) for the outcome variable of reduction in pain. The summary SMD (random effects) was -0.15 (95% CI, -0.35, 0.05). In this outcome, there was no statistical difference between glucosamine and placebo.

27. Comparing GS to placebo in studies using a non-Rotta preparation for WOMAC pain subscale scores: Results from five RCTs were pooled (Cibere 2004; Hughes 2002; Houpt 1999; McAlindon 2004; Zenk 2002). The summary SMD (fixed effects) was 0.01 (95% CI, -0.16, 0.17). In this outcome, there was no statistical difference between glucosamine and placebo.

28. Comparing GS to placebo in studies using a non-Rotta preparation for WOMAC stiffness subscale scores: Result from four RCTs were pooled (Cibere 2004; Houpt 1999; Hughes 2002; Zenk 2002). The summary SMD (fixed effects) was 0.04 (95% CI, -0.18, 0.25). In this outcome, there was no statistical difference between glucosamine and placebo.

29. Comparing GS to placebo in studies using a non-Rotta preparation for WOMAC function subscale scores: Results from four RCTs were pooled (Cibere 2004; Houpt 1999; Hughes 2002; Zenk 2002). The summary SMD (fixed effects) was 0.03 (95% CI, -0.18, 0.25). In this outcome, there was no statistical difference between glucosamine and placebo.

30. Comparing GS or GH to placebo using the Rotta preparation for WOMAC total scores: The summary SMD (fixed effects) for three RCTs (Cibere 2004; Houpt 1999; Zenk 2002) was -0.02 (95% CI, -0.27 to 0.22). In this outcome, there was no statistical difference between glucosamine and placebo.

Toxicity of Glucosamine in OA:

The safety profile of glucosamine in the 20 RCTs was excellent. For example, out of the 1160 subjects randomized to glucosamine treatment in the RCTs, only 41 (4%) were withdrawn because of toxicity. The total number of subjects reporting an adverse reaction was 275 (26%) based on 17 RCTs (n=1045). In the 954 subjects randomized to a placebo group, 49 (5%) were withdrawn because

of toxicity and 270 (32%) reported an adverse reaction (n=846). Therefore, glucosamine was as safe as placebo.

31. Comparing GS or GH to placebo for number of subjects reporting adverse reactions: The summary RR (fixed effects) for fourteen RCTs was 0.97 (95% CI, 0.88 to 1.08).

32. Comparing GS or GH to placebo for number of withdrawals due to toxicity: The summary RR (fixed effects) for seventeen RCTs was 0.82 (95% CI, 0.56 to 1.21).

33. Comparing GS to NSAIDs for number of subjects reporting adverse reactions: The summary RR (fixed effects) for four RCTs was 0.29 (95% CI, 0.19 to 0.44). Therefore, GS was significantly less likely than NSAIDs to produce adverse reactions.

34. Comparing GS to NSAIDs for number of withdrawals due to toxicity: The summary RR (fixed effects) for four RCTs was 0.06 (95% CI, 0.01 to 0.25). Therefore, GS was significantly less likely than NSAIDs to result in withdrawals due to toxicity.

DISCUSSION

The pooled SMD for pain reduction comparing glucosamine to placebo was 0.61, which represents a moderate clinically significant treatment benefit in favour of glucosamine and a relative difference in the change from baseline of 28%. SMD's can be interpreted as effect sizes. Cohen defined an effect size of 0.20 as small, one of 0.50 as moderate, and one of 0.80 or greater as large (Cohen 1977). For function, measured by the Lequesne index, the pooled SMD compared to placebo favoured glucosamine (SMD 0.51 (95% CI, 0.96 to 0.05)). This corresponds to a difference in the change from baseline between glucosamine and placebo of 2.3 units on the Lequesne scale or 21% of baseline. The RCTs comparing GS to an NSAID suggest that GS produces similar symptomatic benefits as NSAIDs, but with a much lower probability of resulting in adverse reactions. These results are very important and suggest that glucosamine therapy may represent a significant breakthrough in the pharmacological management of OA. However, not all outcomes demonstrated a consistent superiority of glucosamine over placebo. For example, neither of the WOMAC outcomes of pain, function and stiffness showed a superiority of glucosamine over placebo. Furthermore, analysis restricted to those studies with adequate allocation concealment did not demonstrate a superiority of glucosamine over placebo for pain and WOMAC function. Therefore, the results in favor of glucosamine are mixed, and further research will still be needed to clarify the true efficacy of glucosamine in OA.

Subgroup analyses of the Rotta preparation showed significant benefit over placebo in terms of pain and the Lequesne index but not in the WOMAC pain, stiffness or function scales. For non-Rotta preparations, the pooled results show that there was no statistically significant difference in terms of pain and WOMAC pain, stiffness and function scales.

Although most of the RCTs show clear superiority of glucosamine over placebo in OA, five RCTs failed to show that glucosamine was better than placebo (Cibere 2004; Houpt 1999; Hughes 2002; McAlindon 2004; Rindone 2000). It is not entirely clear how to reconcile the negative results from these RCTs with the favourable results from the other RCTs (Towheed 2003, McAlindon 2003). However, these five negative RCTs did not use the Rotta brand of GS, and also, had either a limited or no affiliation with a manufacturer of glucosamine. (The trial by McAlindon 2004 did use the Rotta preparation but in only about 10% of the subjects treated with glucosamine). The study by Houpt 1999 was the only RCT that used glucosamine hydrochloride rather than glucosamine sulfate. It is not known if glucosamine hydrochloride is as effective as glucosamine sulfate in the treatment of OA. The study by Rindone 2000 had a mostly male population of enrolled subjects (only 5% were female, which contrasts with the average female inclusion rate in the remaining RCTs of 69%). Furthermore, patients in this study tended to be older and heavier, with a longer duration of OA, and also had a greater degree of radiographic severity than patients evaluated in other RCTs. One additional important aspect of the Rindone 2000 study was that patients who were taking other analgesics at baseline were instructed to continue them for the duration of the study. However, no details are provided with respect to the actual usage of these analgesics during the course of the study or at the end of the study. The use of additional therapeutic interventions may have resulted in less power to be able to detect any significant differences in efficacy. The study by Hughes (Hughes 2002) had almost 50% of the patients taking NSAIDs at baseline and these patients were allowed to continue using these drugs during the course of the trial. Once again, it is possible that the high frequency of additional therapy allowed may have affected the power to be able to detect any significant differences in efficacy.

Perhaps the major limitation with extrapolating the generally favorable results from the glucosamine RCTs lies in the fact that most of the studies (65%) in the Cochrane review evaluated exclusively the prescription medicine made by the Rotta Pharmaceutical Company (a GS preparation that is approved as a prescription drug for OA in the European Union countries). In North America, glucosamine is not considered a conventional prescription drug, rather it is considered as a dietary supplement, which is widely available as an over the counter preparation. Since the content and purity of the various over the counter preparations is known to vary markedly, the relative efficacy and safety of the various preparations may also vary markedly (Adebowale 2000, Deal 1999, Consumer Repts 2002, Russell 2002). Adebowale (Adebowale 2000) analyzed the actual content of glucosamine and chondroitin within several products in the marketplace with the objective of determining if the content deviated from the label claim. The amounts of glucosamine and chondroitin found after analysis were significantly different from the label claims in some products, with deviations from label claims ranging from as low

as 0% to over 115%. Russell (Russell 2002) assessed the content of active ingredients in over the counter GS preparations. The amount of free base varied from 41 to 108% of the mg content stated on the label; the amount of glucosamine varied from 59 to 138% even when expressed as sulfate. These authors concluded that if GS is to be used as a therapeutic agent, it is important that the products conform to a standard in their description.

Glucosamine therapy for OA was found to be relatively well tolerated with a safety profile similar to placebo, but significantly better than NSAIDs. An open study carried out by 252 physicians throughout Portugal evaluated the tolerability of GS in 1208 patients (Tapadinhas 1982). Patients were treated with GS for a mean duration of 50 days (range 13 to 99 days). Eighty-eight (88%) of the study population were free of any adverse effects. In the 12% experiencing adverse effects, the reactions were generally mild in severity and predominantly affected the gastrointestinal tract. All of the reported complaints were reversible after discontinuation of GS.

In a series of letters to the Editor of the *Lancet*, a number of possible adverse reactions with glucosamine were pointed out. Chan (Chan 2001) expressed concern about the potential adverse effects of long term glucosamine therapy on glucose homeostasis, citing evidence that glucosamine may increase insulin resistance and/or impair insulin secretion (Monauni 2000). They also describe a case of a patient with metastatic insulinoma who achieved control of hypoglycemic episodes after starting GS for OA. They cautioned that glucose monitoring is warranted in patients on long-term therapy, and that glucosamine should be used cautiously in patients with diabetes. These concerns have not appeared to be problems in the RCTs, however, they do warrant further investigation and monitoring. A recently published three month RCT further evaluated the possible effects of glucosamine supplementation on glycemic control in a selected population of patients with type 2 diabetes mellitus (Scroggie 2003). The main outcome measure was hemoglobin A1c levels before and after 90 days of therapy. This study demonstrated that oral glucosamine supplementation did not result in clinically significant alterations in glucose metabolism in patients with type 2 diabetes mellitus. A recently published prospective study by Tannis 2004 found that glucosamine supplementation, with normal recommended dosages, did not cause glucose intolerance in healthy adults.

There are additional reports of possible glucosamine related toxicity. Goldstein (Goldstein 2001) speculated that glucosamine may contribute to the development of atherosclerosis by stimulating proteoglycan production by the smooth muscle cells in the arterial wall. Although the theory seems intriguing, there is as yet no experimental or clinical evidence to support its validity. Swinburne (Swinburne 2001) reported the observation that glucosamine has a powerful stimulatory effect on the growth rate and toughness of the nails. The clinical significance of this observation as it pertains to the treatment of OA is not clear. Tallia (Tallia 2002) re-

ported a case of a possible asthma exacerbation associated with use of an oral glucosamine-chondroitin supplement. According to the authors, the cause and effect association in this case could not be confirmed definitively. Matheu (Matheu 1999) reported a case of an immediate hypersensitivity reaction to glucosamine sulfate manifesting with angioedema.

The meta-analysis by McAlindon 2000 provided a useful critical analysis of some of the pertinent methodological concerns associated with the published glucosamine trials. Their main finding was that although glucosamine is likely to be an effective therapy for OA, the actual degree of symptomatic benefit is probably less than that predicted by the available trials. This is because of methodological flaws in many of the published trials. These flaws have been associated with exaggerated estimates of treatment benefit. Methodological flaws identified in the trials included inadequate allocation concealment, absence of intention to treat analyses, and publication bias. Although it seems unlikely, it is still possible that these biases could negate significantly the supposed efficacy of glucosamine. The main difference between this systematic review and the McAlindon review is that this is a Cochrane Review and it includes the comparators as opposed to the glucosamine vs placebo comparison alone. Also, the Cochrane review has been updated as of January 2005.

A more recent meta-analysis was published by Richy 2003 comparing the structural and symptomatic efficacy of glucosamine and chondroitin in relation to placebo. Fifteen placebo-controlled RCTs, published or performed between 1980 and March 2002, were analyzed. The results of this high quality meta-analysis demonstrated that there was a highly significant structural and symptomatic efficacy of glucosamine on all outcomes studied, including joint space narrowing and WOMAC. Safety of glucosamine was excellent and was similar to placebo. The results of our Cochrane review corroborate the results obtained by Richy 2003.

The twelve week study by McAlindon (McAlindon 2004) deserves special mention since it is the only trial that was conducted exclusively over the Internet. Subjects were recruited and followed entirely over the Internet. This is a unique method of conduct of a RCT and the authors have nicely demonstrated the efficiency and methodological aspects of this approach. The study by Cibere (Cibere 2004) also deserves special mention since it is the only trial that was designed as a glucosamine discontinuation trial. All eligible subjects must have been actively using glucosamine for OA for at least one month prior to study entry and they must also have reported having at least a moderate improvement in knee pain since starting on glucosamine. The results of this well conducted study were negative and failed to demonstrate efficacy of continuing glucosamine versus a placebo over a 24 week period.

The mechanisms of action of glucosamine in OA are not known. However, glucosamine is a natural substance and a "building block" of the glycosaminoglycans (GAG) and glycoproteins in

the ground substance of the articular cartilage. In vitro studies have shown that adding GS to human chondrocytes results in increased proteoglycan synthesis (Bassleer 1992, Bassleer 1998; Setnikar 1992). GS has a beneficial effect on animal models of experimental arthritis and may also have anti-inflammatory properties (Conrozier 1998; Setnikar 1991, Setnikar 1991b, Setnikar 2001). It has recently been speculated that the sulfate moiety of GS may actually mediate the clinical benefit of GS in OA (Hoffer 2002).

Pharmacokinetic studies on glucosamine and GS have been carried out primarily by investigators from the Rotta Research Laboratory in Italy (the sponsor of most of the RCTs reviewed here). Early work with ¹⁴C-glucosamine administered IV or orally in the rat indicated that, after IV administration, radioactivity in the plasma declined in the first 30 minutes and reached a peak in the 2nd hour and then started to disappear, with half disappearance at 28 hrs. Radioactivity was detected in all tissues (primarily liver and kidney) and early in skeletal tissues including cartilage (Setnikar 1984). About 50% of the expired ¹⁴C radioactivity appeared as expired CO₂ and 35% in the urine. After oral administration, there was only a small fecal excretion but 85% of the ¹⁴C radioactivity appeared as CO₂, indicating that there was extensive breakdown of the ¹⁴C-glucosamine into smaller fragments. There were no measurements of free ¹⁴C-glucosamine reported in this study.

Pharmacokinetic studies in dog and in man (Setnikar 1986), with IV administered ¹⁴C-GS showed that there was a very rapid disappearance of the radioactivity due to glucosamine ($t_{1/2} = 0.28$ hr) and that this was rapidly replaced by radioactivity originating from the plasma proteins, into which the ¹⁴C-glucosamine and its metabolites are incorporated. Free ¹⁴C-glucosamine was looked for but could not be detected, apparently at any time point, according to this report. The findings were similar with IM administered ¹⁴C-GS (Setnikar 1993). Only a very small proportion of the ¹⁴C radioactivity was found in the femoral cartilage, compared to other organs. In the earlier study by Setnikar et al (Setnikar 1986), large amounts of non-radioactive GS were also administered IV and orally to 6 human volunteers. The ninhydrin amino-acid analyzer method was used for detection of the serum glucosamine (Optica instrument) with a detection limit of about 10 ug/ml. After 800 mg GS administered IV, plasma levels fell rapidly with a first disappearance rate $t_{1/2} = 6.5$ minutes and a terminal rate of $t_{1/2} = 2.1$ hr. However, after oral administration of a single dose of 6000 mg of GS to the human volunteers, plasma glucosamine was below the detection limit at all tested times. It should be noted that the usual oral dosage of GS in the reviewed RCTs was 1500 mg/day. Further studies in six healthy human male volunteers were done with ¹⁴C-GS administered in single doses by the IV, IM and oral routes (Setnikar 1993). After IV administration, the radioactivity due to glucosamine declined rapidly with an initial $t_{1/2}$ of 0.28 hr. After 1-2 hrs, the plasma radioactivity originated entirely from plasma proteins. Less than 1% of the radioactivity was found in the feces, and 28% was found in the urine. The pharmacokinetic

ics of IM administration of ¹⁴C-GS were similar to the IV. Free glucosamine was not detected in the plasma. Much lower levels of radioactivity were found after oral administration apparently due to metabolism to CO₂, water and urea (Setnikar 1993).

Two RCTs have evaluated the ability of glucosamine to protect the cartilage from further loss as defined by changes in radiographic joint cartilage width of the knee (Pavelka 2002; Reginster 2001). These two well conducted prospective three year RCTs showed favourable responses with no significant progression of cartilage loss in subjects assigned to therapy with GS. These RCTs represent the first clinical evidence that glucosamine may indeed modify the natural radiological progression of OA of the knee (Reginster 2003).

The US National Institutes of Health have initiated a large placebo-controlled RCT comparing glucosamine (alone and in combination with chondroitin) to celecoxib and to chondroitin, in patients with symptomatic OA of the knee (Clegg 2003; NIH 1999). Both symptomatic and structural outcomes (i.e. radiological progression) will be studied. Results from this pivotal study are eagerly awaited.

AUTHORS' CONCLUSIONS

Implications for practice

The previous review (December 1999) with 16 studies (12 included in meta-analysis) and 2029 patients showed that glucosamine sulphate taken orally in amounts of 1500 mg/day produced a 60% (percent change from baseline) benefit in pain and increase in function of 33% (percent change in Lequesne index from baseline) in osteoarthritis without side effects.

If only the best designed studies are included, the benefit in pain and WOMAC function is no longer present as shown in this update which includes 20 studies and 2570 patients. Inclusion of eight new studies reduces the overall benefit of pain to 28% and function to 21% in the Lequesne index. Pooled results from studies using a non-Rotta preparation 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 OA. 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.

Some studies suggest the Rotta preparation of glucosamine sulfate may slow radiological progression of OA of the knee over a three year period. The ability of glucosamine to improve symptoms and delay radiological progression of OA affecting other joint sites also needs further research.

Glucosamine was as safe as placebo.

Implications for research

Despite the availability of several RCTs, there are still a number of questions that remain unanswered regarding the use of glucosamine in OA. These questions represent areas for further research. First, are the different glucosamine preparations sold by different manufacturers equally effective (and equally safe) in the therapy of OA? Is GS equally effective to GH? If there any further benefit obtained by using mixed glucosamine preparations that contain additional therapeutic products, such as chondroitin sulfate. Second, why are the trials no longer uniformly positive? Third, is glucosamine helpful for all patients with OA, involving different joints and at different stages of severity? Four, is the dose and route of administration of glucosamine important in maximizing efficacy and minimizing toxicity? Five, how does glucosamine work in the treatment of OA? Six, what are the patient specific predictors of favorable effects on radiological progression of OA?

POTENTIAL CONFLICT OF INTEREST

The current version of the Glucosamine for osteoarthritis review on the Cochrane Library was last revised in 1999. The potential conflicts of interest outlined below have developed since then are being disclosed as the authors have updated the review for this version of the Cochrane Library.

Dr. Tassos Anastasiades submitted patents (Pub. No. US 2002/0045597 A1 and Pub. No. US 6,479,469 B2) for glucosamine type substances in August 2000. The patent protection is for chemically synthesized compounds with substitutions of chain-length larger than the naturally occurring acetyl group in glucosamine.

Dr. Tanveer Towheed was an invited speaker at the November 2002 ACR meeting. The accredited event-a post meeting symposium-was coordinated by the CME department at the Case Western Reserve School of Medicine. Rotta Pharmaceuticals (whose product is glucosamine sulfate) provided an unrestricted educational grant in support of the program. Dr. Towheed presented a review of all available published meta-analyses of various pharmacological therapies for OA. He received a one time honorarium for speaking at this symposium. There is no other association with Rotta pharmaceuticals, or any other potential conflict of interest.

Dr. Joseph Houpt. No information to disclose regarding any potential conflict of interest.

ACKNOWLEDGEMENTS

We would like to thank Jessie McGowan for her assistance in providing the electronic search of the literature. The authors would also like to thank Lindi Jiang for her assistance with data abstraction. Additionally, the authors would like to thank the Cochrane Musculoskeletal Editorial Team for their thoughtful comments and suggestions.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- Queens University Cochrane Network Site. Kingston, Ontario CANADA
- University of Ottawa CANADA

REFERENCES

References to studies included in this review

Cibere 2004 {published data only}

*Cibere J, Kopec JA, Thorne A, Singer J, Canvin J, Robinson DB, et al. Randomized, Double-Blind, Placebo-Controlled Glucosamine Discontinuation Trial in Knee Osteoarthritis. *Arthritis and Rheumatism (Arthritis Care and Research)* 2004;**51**(2):738–745.

Crolle 1980 {published data only}

*Crolle G, D'Este E. Glucosamine sulphate for the management of arthrosis: a controlled clinical investigation. *Current Medical Research & Opinion* 1980;**2**:104–109.

D'Ambrosio 1981 {published data only}

*D'Ambrosio E, Casa B, Bompani R, Scali G, Sclai M. Glucosamine sulphate: a controlled clinical investigation in arthrosis. *Pharmatherapeutica* 1981;**2**(8):504–508.

Drovanti 1980 {published data only}

*Drovanti A, Bignamini AA, Rovati L. Therapeutic activity of oral glucosamine sulfate in osteoarthritis: A placebo-controlled double-blind investigation. *Clinical Therapeutics* 1980;**3**(4):260–272.

Houpt 1999 {published data only}

*Houpt J, McMillan r, Wein C, Paget-Dellio SD. Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. *Journal of Rheumatology* 1999;**26**(11):2423–2430.

Hughes 2002 {published data only}

*Hughes R, Carr A. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatology* 2002;**41**:279–284.

McAlindon 2004 {published data only}

*McAlindon T, Formica M, LaValley M, Lehmer M, Kabbara K. Effectiveness of Glucosamine for symptoms of knee osteoarthritis:

Results from an Internet-based randomized double-blind controlled trial. *American Journal of Medicine* 2004;**117**:643–49.

Muller-FassBender 94 {published data only}

*Muller-Fasbender H, Bach GL, Haase W, Rovati L, Setnikar I. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis and Cartilage* 1994;**2**:61–69.

Noack 1994 {published data only}

*Noack W, Fischer M, Forster K, Rovati L, Setnikar I. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis and Cartilage* 1994;**2**:51–59.

Pavelka 2002 {published data only}

*Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis. A 3-year, randomized, placebo-controlled, double-blind study. *Archives of Internal Medicine* 2002;**162**:2113–2123.

Pujalte 1980 {published data only}

*Pujalte JM, Llavore EP, Ylescupidéz FR. Double-blind clinical trial evaluation of oral glucosamine sulphate in the basic treatment of osteoarthritis. *Current Medical Research and Opinion* 1980;**7**(2):110–114.

Qiu 1998 {published data only}

*Qiu GX, Gao SN, Giacovelli G, Rovati L, setnikar I. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. *Arzneimittelforschung/Drug Resistance Updates* 1998;**48**(1):469–474.

Reginster 2001 {published data only}

Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *Lancet* 2001;**357**:251–256.

Reichelt 1994 {published data only}

*Reichelt A, Forster KK, Fischer M, Rovati L, Setnikar I. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. *Arzneimittelforschung/Drug Resistance Updates* 1994;**44**(1):75–80.

Rindone 2000 {published data only}

*Rindone JB, Hiller D, Collacott E, Nordhaugen N, Arriola G. Randomized, controlled trial of glucosamine for treating osteoarthritis of the knee. *Western Journal of Medicine* 2000;**172**:91–94.

Rovati 1997 {published and unpublished data}

*Rovati LC. The clinical profile of glucosamine sulfate as a selective symptom-modifying drug in osteoarthritis: current data and perspectives. *Osteoarthritis Cartilage* 1997;**5**:72.

Usha 2004 {published data only}

*Usha PR, Naidu MUR. Randomized, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clinical Drug Investigation* 2004;**24**(6):353–63.

Vajjaradul 1981 {published data only}

*Vajjaradul Y. Double-blind clinical evaluation of intra-articular glucosamine in outpatients with gonarthrosis. *Clinical Therapeutics* 1981;**3**(5):336–343.

Vaz 1982 {published data only}

*Vaz AL. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of os-

tearthrosis of the knee in out-patients. *Current Medical Research and Opinion* 1982;**8**:145–9.

Zenk 2002 {published data only}

*Zenk JL, Helmer TR, Kuskowski MA. The effects of milk protein concentrate on the symptoms of osteoarthritis in adults: an exploratory, randomized, double-blind, placebo-controlled trial. *Current Therapeutic Research* 2002;**63**(7):430–442.

References to studies excluded from this review

Braham 2003

Braham R, Dawson B, Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. *British Journal of Sports Medicine* 2003;**37**:45–49.

Magi 1997

*Magi D, Giacovelli G, Rovati LC. Clinical Study on the activity of glucosamine sulfate on osteoarthritis, in comparison with placebo, in patients suffering from osteoarthritis of the knee by means of imaging techniques (NMR, ecotomography, radiology) and computer processing of the such obtained images. Unpublished technical report prepared by Rottapharm 1997.

Pipitone 1997

*Pipitone V, Giacovelli G, Rovati LC. Clinical study on the activity of glucosamine sulfate on the evolution of osteoarthritis in patients with osteoarthritis of the knee. Unpublished technical report prepared by Rottapharm 1997.

Rovati 1993

*Rovati LC, Poma A, Biavati G, et al. A multicenter, randomized, double-blind, parallel-group study to investigate efficacy and safety of oral glucosamine sulfate in osteoarthritis of the spine. Unpublished technical report prepared by Rottapharm 1993.

Additional references

ACR 2000

American College of Rheumatology (ACR) Subcommittee on osteoarthritis guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis and Rheumatism* 2000;**43**:1905–1915.

Adebowale 2000

Adebowale AO, Cox DS, Liang Z, Eddington ND. Analysis of glucosamine and chondroitin sulfate content in marketed products and the caco-2 permeability of chondroitin sulfate raw materials. *Journal of the American Nutraceutical Association* 2000;**3**(1):Spring Issue.

Anderson 2005

Anderson JW, Nicolosi RJ, Borzelleca JF. Glucosamine effects in humans: a review of effects on glucose metabolism, side effects, safety considerations and efficacy. *Food and Chemical Toxicology* 2005;**43**:187–201.

Badley 1995

Badley EM. The effect of osteoarthritis on disability and health care use in Canada. *Journal of Rheumatology* 1995;**22**(suppl 43):19–22.

Barclay 1998

Barclay TS, Tsourounis C, McCart GM. Glucosamine. *Annals of Pharmacotherapy* 1998;**32**:574–579.

- Bassleer 1992**
Bassleer C, Henrotin Y, Franchimont P. In-vitro evaluation of drugs proposed as chondroprotective agents. *International Journal of Tissue Reactions* 1992;**14**:231–241.
- Bassleer 1998**
Bassleer C, Rovati L, Franchimont P. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic cartilage in vitro. *Osteoarthritis Cartilage* 1998;**6**:427–434.
- Bellamy 1997**
Bellamy N, Kirwan J, Boers M, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip and hand osteoarthritis. *Journal of Rheumatology* 1997;**24**:799–802.
- Chan 2001**
Chan NN, Baldeweg S, Tan TM, Hurel S. Glucosamine sulphate and osteoarthritis (letter). *Lancet* 2001;**357**:1617.
- Clegg 2003**
Clegg D. E-mail correspondence updating the current status of the NIH RCT. E-mail June 2003.
- Cohen 1977**
Cohen J. Statistical power analysis for the behavioural sciences. *Statistical power analysis for the behavioural sciences*. New York: Academic Press, 1977.
- Conrozier 1998**
Conrozier T, Mathieu P, Piperno M, et al. Glucosamine sulfate significantly reduced cartilage destruction in a rabbit model of osteoarthritis. *Arthritis and Rheumatism* 1998;**41** (Suppl):S147.
- Consumer Repts 2002**
No authors listed. Joint Remedies. *Consumer Reports* 2002;**67**(1):18–21.
- Creamer 1997**
Creamer P, Hochberg MC. Osteoarthritis. *Lancet* 1997;**350**:503–508.
- Creamer 1998**
Creamer P, Flores R, Hochberg MC. Management of osteoarthritis in older adults. *Clinics in Geriatric Medicine* 1998;**14**(3):434–454.
- Da Camara 1998**
Da Camara C, Dowless GV. Glucosamine sulfate for osteoarthritis. *Annals of Pharmacotherapy* 1998;**32**:580–587.
- Deal 1999**
Deal CL, Moskowitz RW. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate and collagen hydrolysate. *Rheumatic Diseases Clinics of North America* 1999;**25**:379–395.
- Deviere 2002**
Deviere J. Do selective cyclo-oxygenase inhibitors eliminate the adverse events associated with nonsteroidal anti-inflammatory drug therapy?. *European Journal of Gastroenterology and Hepatology* 2002;**14**(Suppl 1):S29–33.
- Felson 1998**
Felson D. Nonmedicinal therapies for osteoarthritis. *Bulletin on the Rheumatic Diseases* 1998;**47**(2):1–7.
- Felson 2000**
Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG. Osteoarthritis: new insights. Part 1: the disease and its prevalence and impact. *Annals of Internal Medicine* 2000;**133**(8):635–646.
- Gabriel 1991**
Gabriel S, Jaakkimainen L, Bombardier C. Risk factors for serious gastrointestinal complications related to use of non-steroidal anti-inflammatory drugs. A meta-analysis. *Annals of Internal Medicine* 1991;**115**:787–796.
- Garner 2002**
Garner S, Fidan D, Frankish R, Judd M, Shea B, Towheed T, Wells G, Tugwell P. Celecoxib for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2002, Issue 4. Art. No.: CD003831. DOI: [10.1002/14651858.CD003831](https://doi.org/10.1002/14651858.CD003831).
- Goldstein 2001**
Goldstein MR. Glucosamine sulphate and osteoarthritis (letter). *Lancet* 2001;**357**:1617–1618.
- Gotzsche 1989**
Gotzsche P. Methodology and overt and hidden bias in reports of 196 double-blind trials of non-steroidal anti-inflammatory drugs in rheumatoid arthritis. *Controlled Clinical Trials* 1989;**10**:31–56.
- Griffin 1991**
Griffin M, Piper J, Daugherty J, et al. Non-steroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. *Annals of Internal Medicine* 1991;**114**:257–263.
- Hedges 1985**
Hedges L, Olkin I. *Statistical methods for meta-analysis*. San Diego, CA: Academic Press, 1995.
- Herman 1986**
Herman J, Appel A, Khosla R, et al. The in vitro effect of select classes of non-steroidal anti-inflammatory drugs on normal cartilage metabolism. *Journal of Rheumatology* 1986;**13**:1014–1018.
- Hochberg 1995a**
Hochberg MC, Altman R, Brandt K, et al. Guidelines for the medical management of osteoarthritis. Part 1. Osteoarthritis of the hip. *Arthritis and Rheumatism* 1995;**38**(11):1535–1540.
- Hochberg 1995b**
Hochberg MC, Altman R, Brandt K, et al. Guidelines for the medical management of osteoarthritis. Part 2. Osteoarthritis of the knee. *Arthritis and Rheumatism* 1995;**38**(11):1541–1547.
- Hochberg 1996**
Hochberg MC, Perlmutter D, Hudson J, et al. Preferences in the management of osteoarthritis of the hip and knee: Results of a survey of community-based rheumatologists in the United States. *Arthritis Care & Research* 1996;**9**(3):170–176.
- Hoffer 2002**
Hoffer LJ, Kaplan LN, Hamadeh MJ, Grigoriu AC, Baron M. Sulfate could mediate the therapeutic effect of glucosamine sulfate. *Metabolism* 2002;**50**(7):767–770.
- Jadad 1996**
Jadad A, Moore A, Carrol D, et al. Assessing the quality of reports of randomized trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1–12.

Lawrence 1998

Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis and Rheumatism* 1998;**41**(5):778–99.

Liang 1984

Liang M, Larsen M, Thomson M, et al. Costs and outcomes in rheumatoid arthritis and osteoarthritis. *Arthritis and Rheumatism* 1984;**27**(5):522–529.

Lozada 1997

Lozada C, Altman R. Chondroprotection in osteoarthritis. *Bulletin on the Rheumatic Diseases* 1997;**46**:5–7.

Matheu 1999

Matheu V, Gracia Bara MT, Pelta R, Vivas E, Rubio M. Immediate-hypersensitivity reaction to glucosamine sulfate. *Allergy* 1999;**54**:643–650.

McAlindon 2000

McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and Chondroitin for Treatment of Osteoarthritis. *JAMA* 2000;**283**(11):1469–1475.

McAlindon 2003

McAlindon T. Why are clinical trials of glucosamine no longer uniformly positive?. *Rheumatic Diseases Clinics of North America* 2003;**29**(4):789–801.

McCarty 1994

McCarty M. The neglect of glucosamine as a treatment for osteoarthritis. A personal perspective. *Medical Hypotheses* 1994;**42**:323–327.

Monauni 2000

Monauni T, Zenti MG, Cretti A, Daniels MC, Targher G, Caruso B, et al. Effects of glucosamine infusion on insulin secretion and insulin action on humans. *Diabetes* 2000;**49**(6):926–935.

Moralestorres 1996

Moralestorres J, Reginster J, Hochberg MC. Rheumatic and musculoskeletal diseases and impaired quality of life. A challenge for rheumatologists. *Journal of Rheumatology* 1996;**23**(1):1–3.

NIH 1999

National Institute of Health. NIH awards study on glucosamine/chondroitin sulfate for knee osteoarthritis (press release). National Institutes of Health: Bethesda, Maryland September 15, 1999.

Petitti 1994

Petitti D. Meta-analysis, Decision analysis, and Cost-Effectiveness analysis. *Monographs in Epidemiology and Biostatistics*. Vol. 24, Oxford University Press, 1994.

Puett 1994

Puett D, Griffin M. Published trials of nonmedicinal and noninvasive therapies for hip and knee osteoarthritis. *Annals of Internal Medicine* 1994;**121**:133–140.

Rashad 1989

Rashad S, Revell P, Hemingway A, et al. Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989;**2**:519–522.

Reginster 2003

Reginster J, Bruyere O, Lecart M, Henrothin Y. Natturocetic (glucosamine and chondroitin sulfate) compounds as structure-modifying drugs in the treatment of osteoarthritis. *Current Opinion in Rheumatology* 2003;**15**(5):651–655.

Richy 2003

Richy F, Bruyere O, Ethgen O, Cucherat M, Henrothin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. A comprehensive meta-analysis. *Archives of Internal Medicine* 2003;**163**:1514–1522.

Roden 1956

Roden L. Effect of hexosamines on the synthesis of chondroitin sulphuric acid in vitro. *Arkiviv Foer Kemi* 1956;**10**:345–352.

Russell 2002

Russell AS, Aghazadeh-Habashi A, Jamali F. Active ingredient consistency of commercially available glucosamine sulfate products. *Journal of Rheumatology* 2002;**29**(11):2407–2409.

Schulz 1995

Schulz KF. Subverting randomization in controlled trials. *JAMA* 1995;**274**(18):1456–1458.

Scott 1993

Scott JC, Hochberg MC. Arthritic and other musculoskeletal diseases. In: Brownson RC, Remington PL, Davis JR editor(s). *Chronic Disease Epidemiology and Control*. Washington: American Public Health Association, 1993.

Scroggie 2003

Scroggie DA, Albright A, Harris MD. The effect of glucosamine-chondroitin supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized controlled trial. *Archives of Internal Medicine* 2003;**163**(13):1587–1590.

Setnikar 1984

Setnikar I, Giachetti C, Zanol G. Absorption, distribution and excretion of radioactivity after a single intravenous or oral administration of ¹⁴C-glucosamine to the rat. *Pharmatherapeutica* 1984;**3**:523–530.

Setnikar 1986

Setnikar I, Giachetti C, Zanol G. Pharmacokinetics of glucosamine in dog and man. *Arzneimittelforschung* 1986;**36**:729–735.

Setnikar 1991

Setnikar I, Pacini M, Revel L. Antiarthritic effects of glucosamine sulfate studied in animal models. *Arzneimittelforschung* 1991;**41**:542–545.

Setnikar 1991b

Setnikar I, Cereda R, Pacini MA, Revel L. Antireactive properties of glucosamine sulfate. *Arzneimittelforschung* 1991;**41**:157–161.

Setnikar 1992

Setnikar I. Antireactive properties of chondroprotective drugs. *International Journal of Tissue Reactions* 1992;**24**:253–261.

Setnikar 1993

Setnikar I, Palumbo R, Canali S, Zanol G. Pharmacokinetics of glucosamine in man. *Arzneimittelforschung* 1993;**43**:1109–1113.

- Setnikar 2001**
Setnikar I, Rovati LC. Absorption, distribution, metabolism and excretion of glucosamine sulfate. *Arzneimittelforschung/Drug Resistance Updates* 2001;**51**(2):699–725.
- Sibbald 2004**
Sibbald B. Rofecoxib (Vioxx) voluntarily withdrawn from market. *Canadian Medical Association Journal* 2004;**171**(9):1027–8.
- Swinburne 2001**
Swinburne LM. Glucosamine sulphate and osteoarthritis (letter). *Lancet* 2001;**357**:1617.
- Tallia 2002**
Tallia AF, Cardone DA. Asthma exacerbation associated with glucosamine-chondroitin supplement. *The Journal of the American Board of Family Practice* 2002;**15**:481–484.
- Tannis 2004**
Tannis AJ, Barban J, Conquer JA. Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentration in healthy individuals. *Osteoarthritis and Cartilage* 2004;**12**(6):506–11.
- Tapadinhas 1982**
Tapadinhas MJ, Rivera IC, Bignamini AA. Oral glucosamine sulphate in the management of arthrosis: report on a multi-centre open investigation in Portugal. *Pharmacotherapeutica* 1982;**3**:157–168.
- Towheed 1997a**
Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the hip. *Journal of Rheumatology* 1997;**24**:549–557.
- Towheed 1997b**
Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. *Seminars in Arthritis and Rheumatism* 1997;**26**:755–770.
- Towheed 1998**
Towheed TE. Impact of musculoskeletal disorders in Canada. *Annals of the Royal College of Physicians and Surgeons of Canada* 1998;**31**(5):229–232.
- Towheed 1999**
Towheed TE, Anatassiades TP. Glucosamine therapy for osteoarthritis (editorial). *Journal of Rheumatology* 1999;**26**(11):2294–2297.
- Towheed 2000**
Towheed TE. Glucosamine and chondroitin for treating symptoms of osteoarthritis: evidence is widely touted but incomplete. *JAMA* 2000;**283**(11):1483–1484.
- Towheed 2002**
Towheed TE. Published meta-analyses of pharmacological therapies for osteoarthritis. *Osteoarthritis Cartilage* 2002;**10**(11):836–837.
- Towheed 2003**
Towheed TE. Current Status of glucosamine therapy in osteoarthritis. *Arthritis and Rheumatism* 2003;**49**(4):601–604.
- Vidal 1978**
Vidal Y, Plana R, Bizzarri D, et al. Articular cartilage pharmacology. In vitro studies on glucosamine and non-steroidal anti-inflammatory drugs. *Pharm Res Comm* 1978;**10**:557.
- Wright 2002**
Wright JM. The double-edged sword of COX-2 selective NSAIDs. *Canadian Medical Association Journal* 2002;**167**(10):1131–1137.

* Indicates the major publication for the study

TABLES

Characteristics of included studies

Study	Cibere 2004
Methods	Randomized Controlled Trial Double Blinded Discontinuation Trial Multicentre trial Parallel group
Participants	Outpatients with OA of the knee Country: Canada N=137 In order to qualify for study entry, subjects must have been users of glucosamine and have experienced at least a moderate improvement in knee pain since starting on glucosamine Mean age = 64.5 years Female 60%

Characteristics of included studies (*Continued*)

	Male 40%
Interventions	GS=1500 mg/day vs placebo for 24 weeks
Outcomes	Proportion of disease flares Time to disease flare and severity of disease flare WOMAC pain WOMAC stiffness WOMAC function WOMAC total Analgesic medication usage
Notes	Quality Score= Design=8/8 Analysis=6/8 Total=14/16 Jadad Score/5 Randomization 1+1 Double-blinded 1+1 Withdrawals 1 Quality score=5
Allocation concealment	A – Adequate

Study	Crolle 1980
Methods	Randomized Controlled Trial Double Blinded Single Centre Parallel group
Participants	Inpatients with osteoarthritis Country:Italy N=30 mean age 72.7 years Female 73% Male 27%
Interventions	GS=400 mgs OD IM (12) IA (3) q7days followed by GS=500 mgs gms TID versus IM OD (piperazine plus chlorbutanol) x 7days followed two weeks of oral placebo Duration=3 weeks
Outcomes	Pain (at rest) Pain (active range of motion) Pain (passive range of motion) scored from 0-3 scale Restricted function, time to walk 20 metres Safety
Notes	Quality Score = Design=2/8 Analysis=7/8 Total 9/16 Jadad Score /5 Randomized = 1

Characteristics of included studies (Continued)

	Double Blind = 1+1 Withdrawals = 0 Quality Score = 3
Allocation concealment	C – Inadequate
Study	D'ambrosio 1981
Methods	Randomized Controlled Trial Double Blinded Single Centre Parallel group
Participants	Inpatients with chronic degenerative osteoarthrosic disorders (site not specified) Country:Italy N= 30 Mean age=74.7 years Female: 77% Male: 23%
Interventions	GS 400 mgs OD (IV or IM) for 7 days followed by two weeks of GS 500 mgs PO TID versus (piperazine plus chlorbutanol) x 7days followed two weeks of oral placebo Duration:3 weeks
Outcomes	Pain (at rest) Pain (during passive range of motion) Pain (active range of motion) 0-3 scale Functional limitation 0-3 scale Safety
Notes	Quality Score = Design=2/8 Analysis=7/8 Total 9/16 Jadad Score /5 Randomized = 1 Double Blind = 1+1 Withdrawals = 0 Quality Score = 3
Allocation concealment	C – Inadequate

Study	Drovanti 1980
Methods	Randomized Controlled Trial Double Blinded Single Centre Parallel group
Participants	Inpatients with osteoarthritis at multiple sites Country :Italy N= 80 Mean age: 60 years Female:78%

Characteristics of included studies (*Continued*)

	Male:22%
Interventions	GS 500 mgs PO TID versus placebo PO TID Duration: 4 weeks
Outcomes	Pain (0-4 scale) Joint tenderness Swelling Restriction of active movement and restriction of passive movement Physician global rating Safety
Notes	Quality Score = Design=0/8 Analysis=7/8 Total 7/16 Jadad Score /5 Randomized = 1 Double Blind = 1+1 Withdrawals = 0 Quality Score = 3
Allocation concealment	C – Inadequate

Study	Houpt 1999
Methods	Randomized Controlled Trial Double Blinded Single Centre Parallel group
Participants	Outpatients with primary osteoarthritis of the knee Country :Canada N= 118 Mean age: 64.5 years Female:62% Male:38% Age range: 40-85 years
Interventions	GH 500 mgs PO TID versus placebo PO TID Duration: 8 weeks with an additional 8 weeks followup period (open label)
Outcomes	WOMAC Daily pain diary Global patient derived Improvement on knee examination use of acetaminophen Perception as to what group the subject were randomized to Safety
Notes	Quality Score = Design=7/8 Analysis=6/8 Total 13/16 Jadad Score: Randomized = 1 Double Blind = 2

Characteristics of included studies (*Continued*)

Withdrawals = 0
 Extra Point = 0
 Quality Score = 3

Allocation concealment A – Adequate

Study **Hughes 2002**

Methods Randomized Controlled Trial
 Double Blinded
 Single Centre
 Parallel Group

Participants Outpatients with osteoarthritis of the knee
 Country: UK
 N=80
 Mean age=62.3 years
 Female=68%
 Male=32%

Interventions GS 500 mg po tid versus placebo po tid
 Duration: 6 months

Outcomes VAS global pain
 VAS pain on movement
 VAS pain at rest
 WOMAC pain
 WOMAC stiffness
 WOMAC function
 McGill Pain Questionnaire (Affective)
 McGill Pain Questionnaire (Sensory)
 OARSI Response Criteria
 Knee range of motion

Notes Quality Score=
 Design=5/8
 Analysis=5/8
 Total=10/16

 Jadad Score /5
 Randomized=1+1
 Double Blinded=1+1
 Withdrawals=1
 Quality Score=5

Allocation concealment A – Adequate

Study **McAlindon 2004**

Methods Randomized Controlled Internet Conducted Trial
 Double Blinded
 Single Centre
 Parallel Group

Participants Outpatients with osteoarthritis of the knee
 Country: USA
 N=205
 Mean age=NA

Characteristics of included studies (Continued)

	64% female 36% male
Interventions	GS 1500 mg/day vs placebo Duration: 12 weeks
Outcomes	WOMAC pain WOMAC stiffness WOMAC function WOMAC total Changes in analgesic usage
Notes	Quality Score= Design=5/8 Analysis=7/8 Total=12/16 Jadad Score Randomization 1+1 Double-blinded 1+1 Withdrawals 1 Total 5/5
Allocation concealment	A – Adequate

Study Muller-FassBender 94

Methods	Randomized Controlled Trial Double Blinded MultiCentre Parallel group
Participants	Inpatients with active osteoarthritis of the knee Country :Germany N= 200 Mean age: 54 years Female:48% Male:52%
Interventions	GS 500 mgs PO TID versus Ibuprofen 400 PO TID Duration: 4 weeks
Outcomes	Lequesne Index Global investigator derived Safety
Notes	Quality Score = Design=5/8 Analysis=7/8 Total 12/16 Jadad Score /5 Randomized = 1+1 Double Blind = 1+1 Withdrawals = 1 Quality Score = 5
Allocation concealment	A – Adequate

Study Noack 1994

Methods	Randomized Controlled Trial
---------	-----------------------------

Characteristics of included studies (Continued)

	Double Blinded MultiCentre Parallel group
Participants	Outpatients with osteoarthritis of the knee Country :Germany N= 252 Mean age: 55 years Female:60% Male:40%
Interventions	GS 500 MGS PO TID versus placebo PO TID Duration: 4 weeks
Outcomes	Lequesne Index Global investigator derived Safety
Notes	Quality Score = Design=5/8 Analysis=7/8 Total 12/16 Jadad Score /5 Randomized = 1+1 Double Blind = 1+1 Withdrawals = 1 Quality Score = 5
Allocation concealment	A – Adequate

Study	Pavelka 2002
Methods	Randomized Controlled Trial Double Blinded Parallel Group Single Centre
Participants	Outpatients with osteoarthritis of the knee Country: Prague, Czech Republic N=202 Mean age=62.3 years Female=78% Male=22%
Interventions	GS 1500 mg po od versus placebo po od Duration: 3 years
Outcomes	WOMAC pain WOMAC stiffness WOMAC function WOMAC total Lequesne Index Joint space narrowing (x-ray)
Notes	Quality Score= Design=6/8 Analysis=7/8 Total=13/16

Characteristics of included studies (Continued)

Jadad Score /5
 Randomized = 1+1
 Double Blind=1+1
 Withdrawals=1
 Quality Score =5

Allocation concealment A – Adequate

Study	Pujalte 1980
Methods	Randomized Controlled Trial Double Blinded Single Centre Parallel group
Participants	Outpatients with established osteoarthritis of the knee Country :Phillipines N= 20 Mean age: 61.7 years Female:85% Male:15%
Interventions	GS 500 MGS PO TID versus placebo PO TID Duration: 8 weeks
Outcomes	Articular pain (1-4 scale) Joint tenderness (1-4 scale) Joint swelling (1-4 scale) Restricted movement (1-4 scale) Global investigator derived Safety
Notes	Quality Score = Design=2/8 Jadad Score /5 Randomized = 1 Double Blind = 1+1 Withdrawals = 1 Quality Score = 4 Analysis=5/8 Total 7/16
Allocation concealment	C – Inadequate

Study	Qiu 1998
Methods	Randomized Controlled Trial Double Blinded MultiCentre Parallel group
Participants	Outpatients with osteoarthritis of the knee Country :China N= 178 Mean age: 56.4 years Female:79%

Characteristics of included studies (*Continued*)

	Male:21%
Interventions	GS 500 mgs PO TID versus Ibuprofen 400 PO TID Duration: 4 weeks of treatment and two weeks of followup
Outcomes	Knee pain (at rest, movement, tenderness) (0-3 scale) Knee swelling (0-3 scale) Global investigator derived Safety
Notes	Quality Score = Design=0/8 Analysis=4/8 Total 4/16 Jadad Score /5 Randomized = 1 Double Blind = 1+1 Withdrawals = 1 Quality Score = 4
Allocation concealment	C – Inadequate

Study	Reginster 2001
Methods	Randomized Controlled Trial Double Blinded Parallel Group Single Centre
Participants	Outpatients with osteoarthritis of the knee Country: Belgium N = 212 Mean age 65.8 years Female=76% Male=24%
Interventions	GS 1500 mg po od versus placebo po od Duration: 3 years
Outcomes	WOMAC pain WOMAC stiffness WOMAC function Mean joint space narrowing (x-ray) Minimum joint space narrowing (x-ray) WOMAC total
Notes	Quality Score = Design=5/8 Analysis=7/8 Total=12/16 Jadad Score Randomized =1+1 Double Blind=1 Withdrawals=1 Quality Score=4
Allocation concealment	A – Adequate

Characteristics of included studies (Continued)

Study	Reichelt 1994
Methods	Randomized Controlled Trial Double Blinded MultiCentre Parallel group
Participants	Outpatients with osteoarthritis of the knee Country :Germany N= 155 Mean age: 56.5 years Female:65% Male:35%
Interventions	GS 400 mgs IM x two per week versus placebo IM x two per week Duration: 6 weeks of treatment and two weeks of followup
Outcomes	Lequesne Index Global investigator derived Safety
Notes	Quality Score = Design=3/8 Analysis=7/8 Total 10/16 Jadad Score /5 Randomized = 1 Double Blind = 1+1 Withdrawals = 1 Quality Score = 4
Allocation concealment	C – Inadequate

Study	Rindone 2000
Methods	Randomized Controlled Trial Double Blinded Parallel Group Single Centre
Participants	Outpatients with osteoarthritis of the knee Country: USA N=114 Female=5% Male=95%
Interventions	GS 500 mg po tid versus placebo po tid Duration: 2 months
Outcomes	VAS pain at rest VAS pain while walking
Notes	Quality Score= Design=3/8 Analysis=4/8 Total=7/16 Jadad Score /5 Randomized=1+1

Characteristics of included studies (Continued)

	Double Blinded=1 Withdrawals=0 Quality Score=3
Allocation concealment	C – Inadequate
Study	Rovati 1997
Methods	Randomized Controlled Trial Double Blinded Multicentre Parallel group This study is unpublished at this time (The authors' have provided us data from this study in the form of a full manuscript) Preliminary data from the study were also presented in abstract form by Rovati LC, 1997
Participants	Outpatients with primary osteoarthritis of the knee Country: France N =319 Mean age 65.5 years Female=75% Male=25% Age range= 45-85 years
Interventions	GS=1500 mgs per day versus piroxicam 20 mgs per day versus the combination of the two versus double placebo Duration 12 weeks of treatment and 8 weeks of followup
Outcomes	Lequesne Index Pain (VAS) Safety
Notes	Quality Score = Design=5/8 Analysis=8/8 Total 13/16 Jadad Score /5 Randomized = 1+1 Double Blind = 1+1 Withdrawals = 1 Quality Score = 5
Allocation concealment	A – Adequate

Study	Usha 2004
Methods	Randomized Controlled Trial Double Blinded Parallel Group Single Centre
Participants	Outpatients with mild to moderate osteoarthritis of the knee. Country: India N=118 Mean age=51 years 60% female, 40% male
Interventions	GS vs MSM vs GS+MSM vs placebo Duration: 12 weeks

Characteristics of included studies (Continued)

Outcomes	Pain, Lequesne Index, walk time, joint swelling, usage of rescue analgesics, global patient, global investigator
Notes	Quality Score= Design=3/8 Analysis=7/8 Total=10 Jadad Score Randomized 1 Double blinded 1 +1 withdrawals 1 Total 4/5
Allocation concealment	C – Inadequate

Study Vajradul 1981

Methods	Controlled Trial (query randomized) Double Blinded MultiCentre Parallel group
Participants	Outpatients with osteoarthritis of the knee Country :Thailand N= 60 Mean age: 52.6 years Female:83% Male:17%
Interventions	GS IA weekly versus placebo IA weekly Duration: 5 weeks and 4 weeks followup
Outcomes	Pain spontaneous (0-2 scale) Pain on standing (0-2 scale) Pain on walking (0-2 scale) Range of motion Time to climb five steps Knee joint circumference Safety
Notes	Quality Score = Design=2/8 Analysis=6/8 Total 8/16 Jadad Score /5 Randomized = 0 Double Blind = 1+1 Withdrawals = 1 Quality Score = 3
Allocation concealment	C – Inadequate

Study Vaz 1982

Methods	Randomized Controlled Trial Double Blinded
---------	--

Characteristics of included studies (Continued)

	Single Centre Parallel group
Participants	Outpatients with osteoarthritis of the knee Country :Portugal N= 40 Mean age: 57.8 years Female:74% Male:26%
Interventions	GS 500 mgs PO TID versus Ibuprofen 400 PO TID Duration: 8 weeks
Outcomes	Articular pain (0-3 scale) Swelling Global investigator derived
Notes	Quality Score = Design=0/8 Analysis=6/8 Total 6/16 Jadad Score /5 Randomized = 1 Double Blind = 1 Withdrawals = 1 Quality Score = 3
Allocation concealment	C – Inadequate

Study	Zenk 2002
Methods	Randomized Controlled Trial Double Blinded Parallel Group Single Centre
Participants	Outpatients with osteoarthritis of the knee and/or hip Country: USA N=42 Mean age=59 years Female=81% Male=19%
Interventions	GS 500 mg po tid versus placebo versus milk protein concentrate 2000 mg po bid Duration: 6 weeks
Outcomes	WOMAC pain WOMAC stiffness WOMAC function WOMAC total
Notes	Quality Score= Design=5/8 Analysis=6/8 Total=11/16 Jadad Score /5 Randomized=1 Double Blinded=1+1

Withdrawals=1
Quality Score=4

Allocation concealment A – Adequate

GS=Glucosamine sulfate

GH=Glucosamine hydrochloride

OD=per day

IM=Intramuscular

IA=intrarticular

IV=Intravenous

TID = three times per day

PO=oral

WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

OARSI=Osteoarthritis Research Society International Responder Criteria

MSM=methylsulfonylmethane

NA=not available

Characteristics of excluded studies

Study	Reason for exclusion
Braham 2003	This RCT compared glucosamine to placebo in subjects who experience regular knee pain. However, the cause of the knee pain was not clearly established, and may possibly not have been caused by OA of the knee.
Magi 1997	Unpublished brief technical report prepared by Rottapharm primarily for regulatory authorities. Report describes a pilot long-term feasibility study in subjects with OA of the knee. This was a phase 3 RCT.
Pipitone 1997	Unpublished brief technical report prepared by Rottapharm primarily for regulatory authorities. Report describes a pilot long-term feasibility study in subjects with OA of the knee. This was a phase 3 RCT.
Rovati 1993	Unpublished brief technical report prepared by Rottapharm primarily for regulatory authorities. Report describes a pilot short-term in subjects with OA of the spine. This was a phase 3 RCT. Some of the data from this study was published in abstract form by Foerster KK in the 2000 September Supplemental Issue of Arthritis and Rheumatism.

ANALYSES

Comparison 01. Glucosamine versus placebo

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain	15	1481	Standardised Mean Difference (Random) 95% CI	-0.61 [-0.95, -0.28]
02 Lequesne Index	4	741	Standardised Mean Difference (Random) 95% CI	-0.51 [-0.96, -0.05]
03 Lequesne Index	2	407	Relative Risk (Fixed) 95% CI	1.52 [1.20, 1.91]
04 WOMAC Pain Subscale	7	955	Standardised Mean Difference (Fixed) 95% CI	-0.04 [-0.17, 0.09]
05 WOMAC Stiffness Subscale	5	538	Standardised Mean Difference (Fixed) 95% CI	-0.06 [-0.23, 0.11]
06 WOMAC Function Subscale	6	750	Standardised Mean Difference (Fixed) 95% CI	-0.07 [-0.21, 0.08]
07 WOMAC Total	5	672	Standardised Mean Difference (Fixed) 95% CI	-0.15 [-0.30, 0.00]
08 Mean Joint Space Width	1	212	Standardised Mean Difference (Fixed) 95% CI	0.07 [-0.20, 0.34]
09 Minimum Joint Space Width	2	414	Standardised Mean Difference (Fixed) 95% CI	0.24 [0.04, 0.43]
10 Osteoarthritis Research Society International Responder Criteria (OARSI)	1	78	Relative Risk (Fixed) 95% CI	0.92 [0.48, 1.76]

11 Toxicity (Number of Patients Reporting Adverse Events)	14	1685	Relative Risk (Fixed) 95% CI	0.97 [0.88, 1.08]
12 Toxicity (Number of Withdrawals due to Adverse Events)	17	1908	Relative Risk (Fixed) 95% CI	0.82 [0.56, 1.21]

Comparison 02. Glucosamine versus NSAIDs [Piroxicam, Ibuprofen]

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain	3	362	Standardised Mean Difference (Fixed) 95% CI	-0.40 [-0.60, -0.19]
02 Lequesne Index	2	345	Standardised Mean Difference (Random) 95% CI	-0.36 [-1.07, 0.35]
03 Toxicity (Number of Patients Reporting Adverse Events)	4	580	Relative Risk (Fixed) 95% CI	0.29 [0.19, 0.44]
04 Toxicity (Number of Withdrawals due to Adverse Events)	4	580	Relative Risk (Fixed) 95% CI	0.06 [0.01, 0.25]

Comparison 03. Glucosamine versus placebo (Allocation concealment A)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain	8	1111	Standardised Mean Difference (Random) 95% CI	-0.19 [-0.50, 0.11]
02 Lequesne Index	3	599	Standardised Mean Difference (Random) 95% CI	-0.61 [-1.21, -0.01]
03 Lequesne Index	1	252	Relative Risk (Fixed) 95% CI	1.43 [1.08, 1.91]
04 WOMAC Pain Subscale	7	955	Standardised Mean Difference (Fixed) 95% CI	-0.04 [-0.17, 0.09]
05 WOMAC Stiffness Subscale	5	538	Standardised Mean Difference (Fixed) 95% CI	-0.06 [-0.23, 0.11]
06 WOMAC Function Subscale	6	750	Standardised Mean Difference (Fixed) 95% CI	-0.07 [-0.21, 0.08]
07 WOMAC Total	5	672	Standardised Mean Difference (Fixed) 95% CI	-0.15 [-0.30, 0.00]
09 Minimum Joint Space Width	2	414	Standardised Mean Difference (Fixed) 95% CI	0.24 [0.04, 0.43]
11 Toxicity (Number of Patients Reporting Adverse Events)	7	1208	Relative Risk (Fixed) 95% CI	0.97 [0.88, 1.08]
12 Toxicity (Number of Withdrawals due to Adverse Events)	9	1373	Relative Risk (Fixed) 95% CI	0.78 [0.52, 1.18]

Comparison 04. Glucosamine versus placebo (Rotta preparation)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain	7	730	Standardised Mean Difference (Random) 95% CI	-1.31 [-1.99, -0.64]
02 Lequesne Index	4	741	Standardised Mean Difference (Random) 95% CI	-0.51 [-0.96, -0.05]
03 Lequesne Index	2	407	Relative Risk (Fixed) 95% CI	1.52 [1.20, 1.91]
04 WOMAC Pain Subscale	2	414	Standardised Mean Difference (Fixed) 95% CI	-0.10 [-0.29, 0.09]
05 WOMAC Stiffness Subscale	1	202	Standardised Mean Difference (Fixed) 95% CI	-0.22 [-0.50, 0.06]
06 WOMAC Function Subscale	2	414	Standardised Mean Difference (Fixed) 95% CI	-0.14 [-0.34, 0.05]

07 WOMAC Total 2 414 Standardised Mean Difference (Fixed) 95% CI -0.23 [-0.42, -0.03]

Comparison 05. Glucosamine versus placebo (non-Rotta preparation)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain	8	751	Standardised Mean Difference (Random) 95% CI	-0.15 [-0.35, 0.05]
02 WOMAC Total	3	258	Standardised Mean Difference (Fixed) 95% CI	-0.02 [-0.27, 0.22]
04 WOMAC Pain Subscale	5	541	Standardised Mean Difference (Fixed) 95% CI	0.01 [-0.16, 0.17]
05 WOMAC Stiffness Subscale	4	336	Standardised Mean Difference (Fixed) 95% CI	0.04 [-0.18, 0.25]
06 WOMAC Function Subscale	4	336	Standardised Mean Difference (Fixed) 95% CI	0.03 [-0.18, 0.25]

INDEX TERMS

Medical Subject Headings (MeSH)

Double-Blind Method; Glucosamine [*therapeutic use]; Osteoarthritis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans

COVER SHEET

Title	Glucosamine therapy for treating osteoarthritis
Authors	Towheed TE, Maxwell L, Anastassiades TP, Shea B, Houpt J, Robinson V, Hochberg MC, Wells G
Contribution of author(s)	<p>TT is responsible for the overall content of this review</p> <p>TP did data abstraction and quality assessment and reviewed the inclusion criteria for selected trials and wrote some of the discussion regarding the pharmacokinetics of glucosamine</p> <p>LM did data abstraction, assisted with data analysis and helped with the preparation of the final version</p> <p>JH critically reviewed the results and helped to draft the final version of this review</p> <p>BS was involved in quality assessment</p> <p>VW provided analytic support, helped in the preparation of the final document and reviewed the final version.</p> <p>MH critically reviewed the results and helped to draft the final version of this review</p> <p>GW provided methodological and statistical support</p>
Issue protocol first published	/
Review first published	2000/1
Date of most recent amendment	11 February 2008
Date of most recent SUBSTANTIVE amendment	23 February 2005
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author

Date new studies found and included/excluded Information not supplied by author

Date authors' conclusions section amended Information not supplied by author

Contact address Dr Tanveer Towheed
Assistant Professor
Medicine and of Community Health and Epidemiology
Queen's University
Etherington Hall-Room 2066
Kingston
Ontario
K7L 3N6
CANADA
E-mail: tt5@post.queensu.ca
Tel: + 1 613 545 6896
Fax: +1 613 545 2189

DOI 10.1002/14651858.CD002946.pub2

Cochrane Library number CD002946

Editorial group Cochrane Musculoskeletal Group

Editorial group code HM-MUSKEL

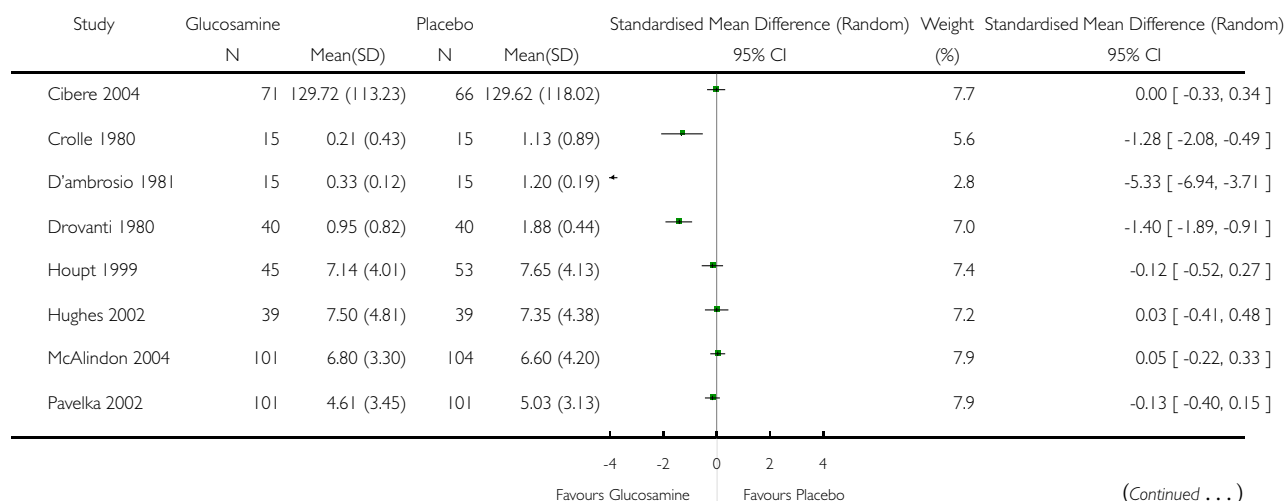
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Glucosamine versus placebo, Outcome 01 Pain

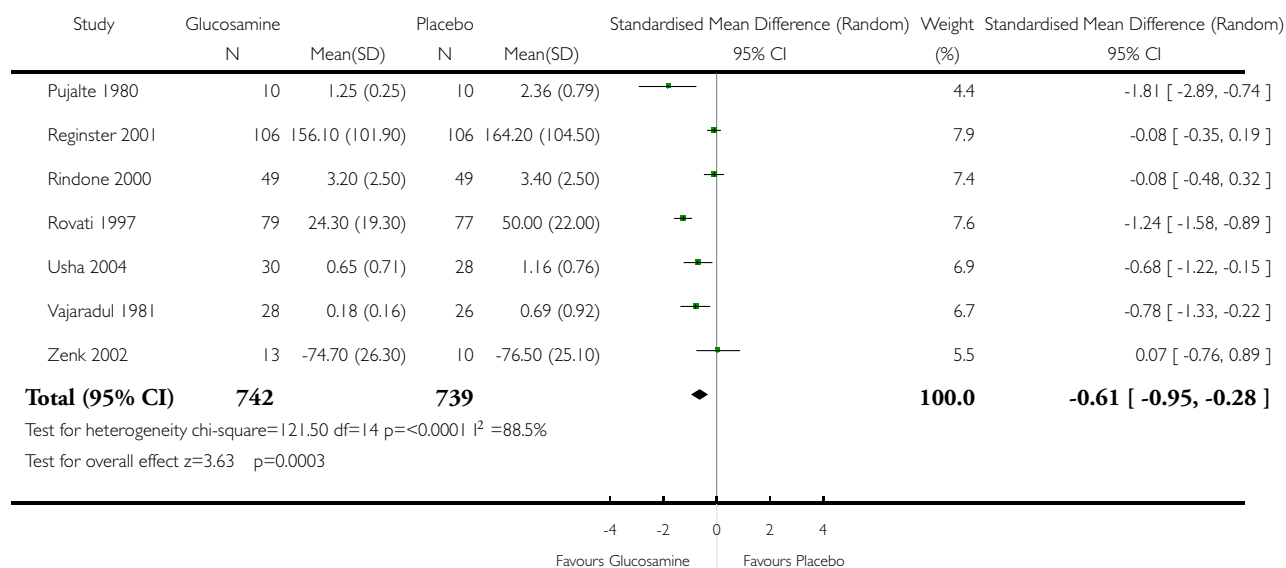
Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 01 Pain



(... Continued)

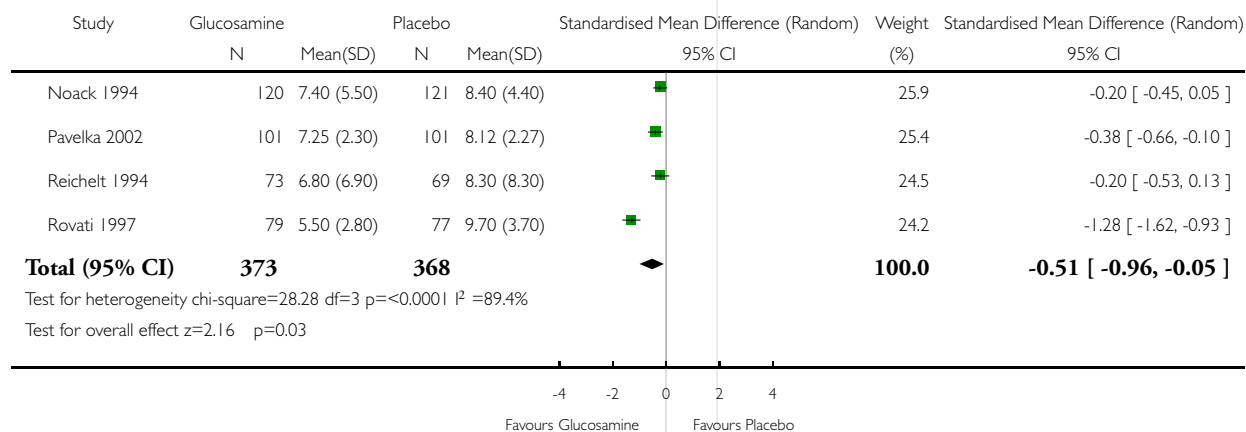


Analysis 01.02. Comparison 01 Glucosamine versus placebo, Outcome 02 Lequesne Index

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 02 Lequesne Index

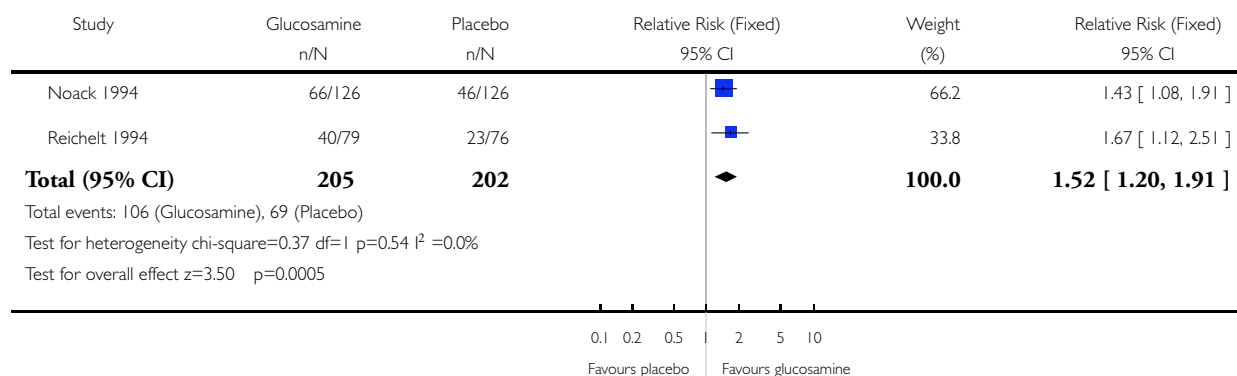


Analysis 01.03. Comparison 01 Glucosamine versus placebo, Outcome 03 Lequesne Index

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 03 Lequesne Index

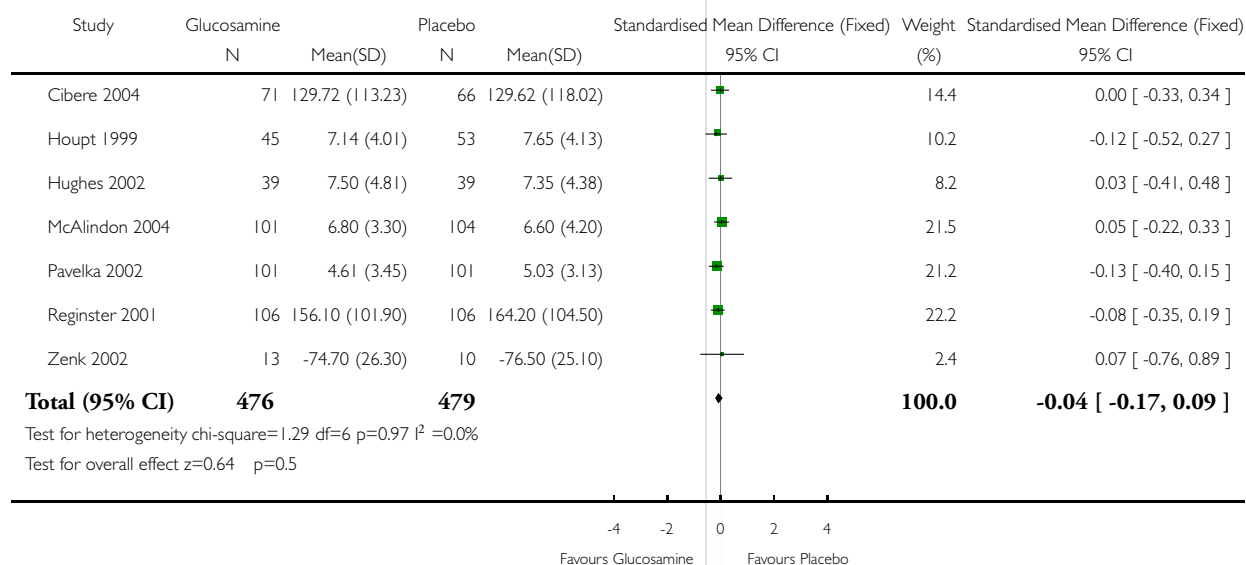


Analysis 01.04. Comparison 01 Glucosamine versus placebo, Outcome 04 WOMAC Pain Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 04 WOMAC Pain Subscale

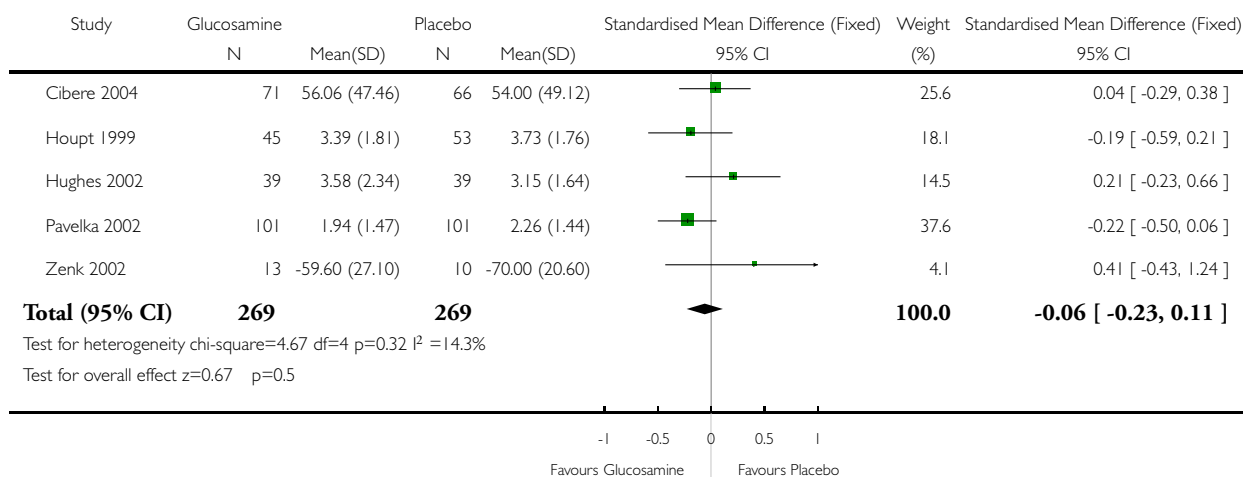


Analysis 01.05. Comparison 01 Glucosamine versus placebo, Outcome 05 WOMAC Stiffness Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 05 WOMAC Stiffness Subscale

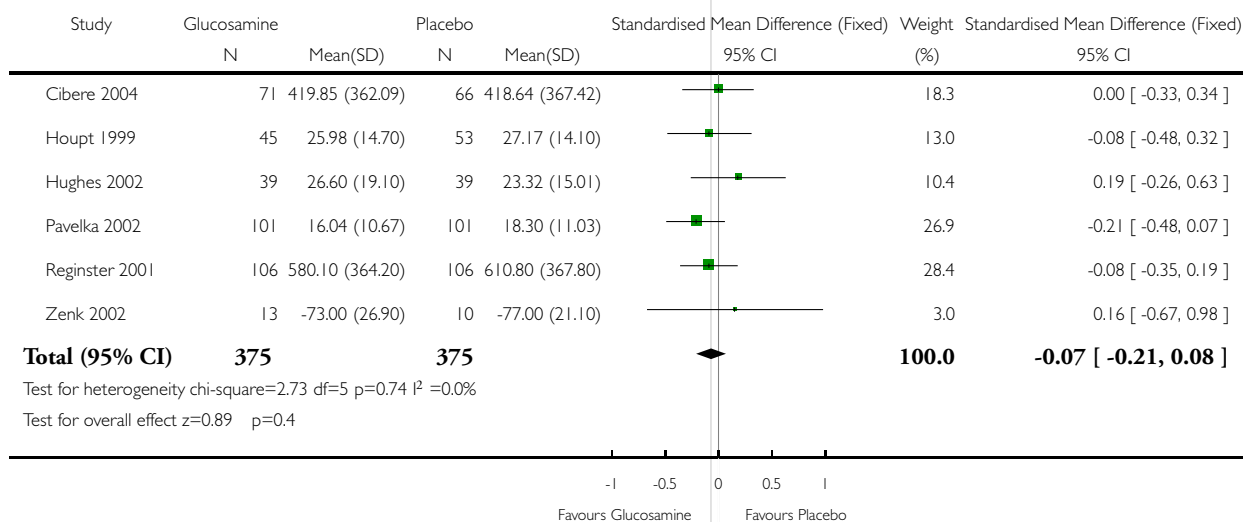


Analysis 01.06. Comparison 01 Glucosamine versus placebo, Outcome 06 WOMAC Function Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 06 WOMAC Function Subscale

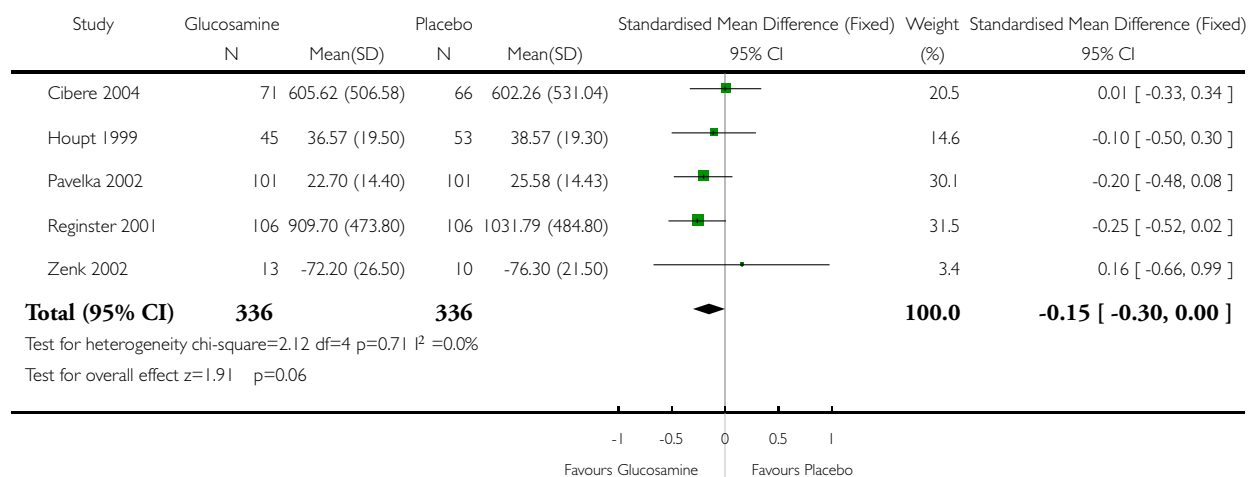


Analysis 01.07. Comparison 01 Glucosamine versus placebo, Outcome 07 WOMAC Total

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 07 WOMAC Total

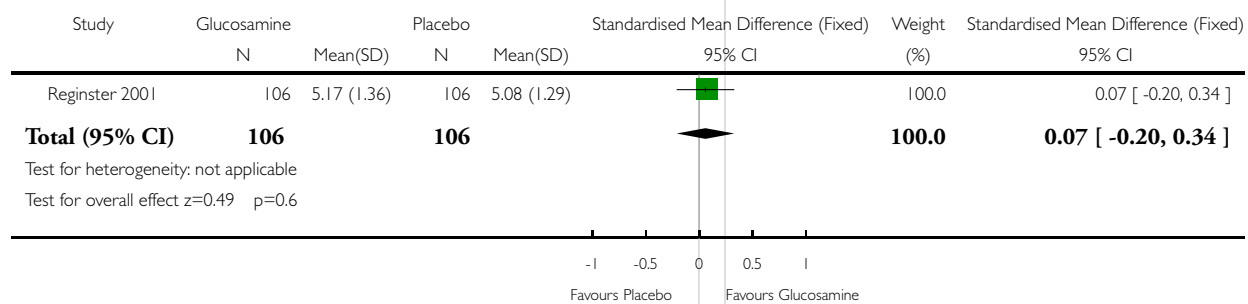


Analysis 01.08. Comparison 01 Glucosamine versus placebo, Outcome 08 Mean Joint Space Width

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 08 Mean Joint Space Width

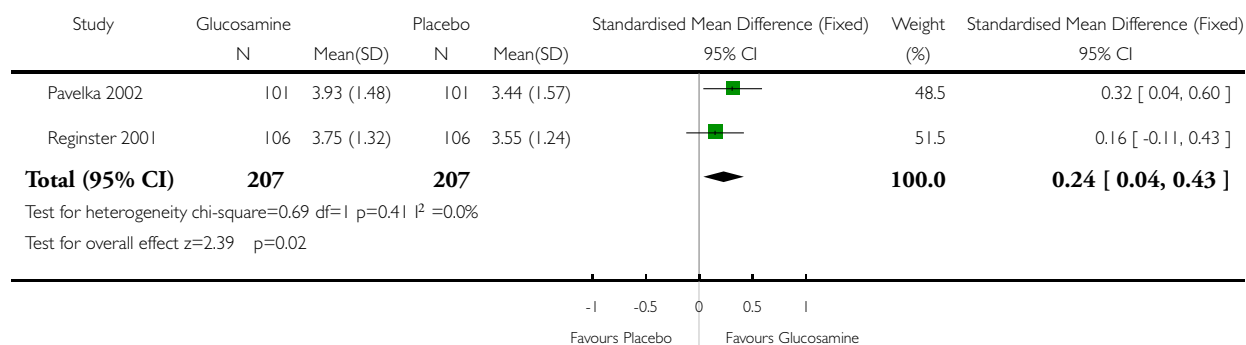


Analysis 01.09. Comparison 01 Glucosamine versus placebo, Outcome 09 Minimum Joint Space Width

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 09 Minimum Joint Space Width

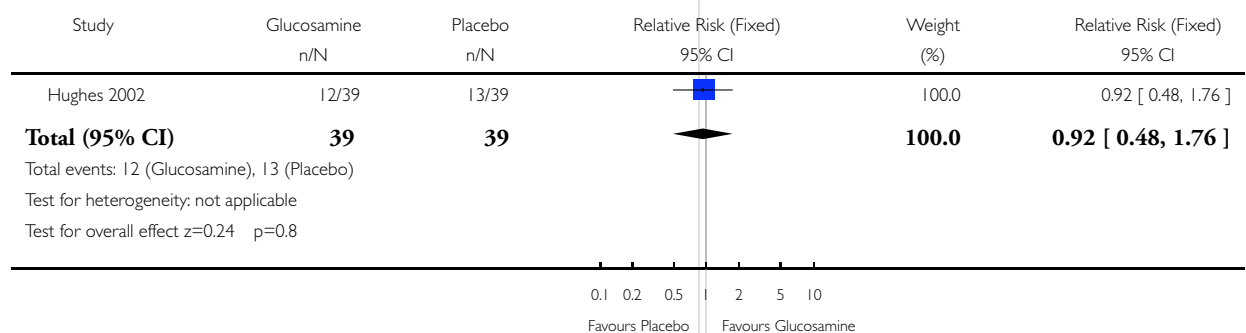


Analysis 01.10. Comparison 01 Glucosamine versus placebo, Outcome 10 Osteoarthritis Research Society International Responder Criteria (OARSI)

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 10 Osteoarthritis Research Society International Responder Criteria (OARSI)

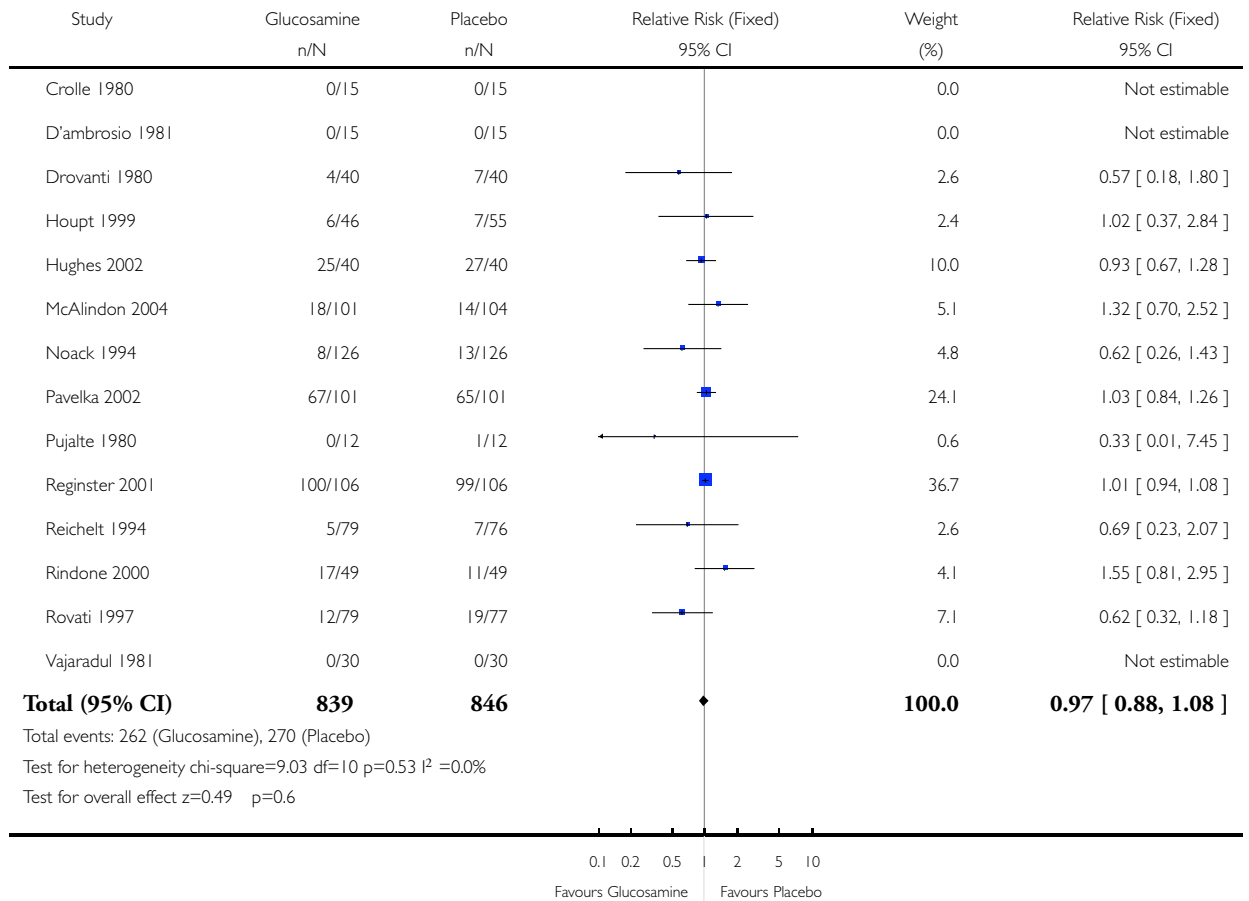


Analysis 01.11. Comparison 01 Glucosamine versus placebo, Outcome 11 Toxicity (Number of Patients Reporting Adverse Events)

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 11 Toxicity (Number of Patients Reporting Adverse Events)

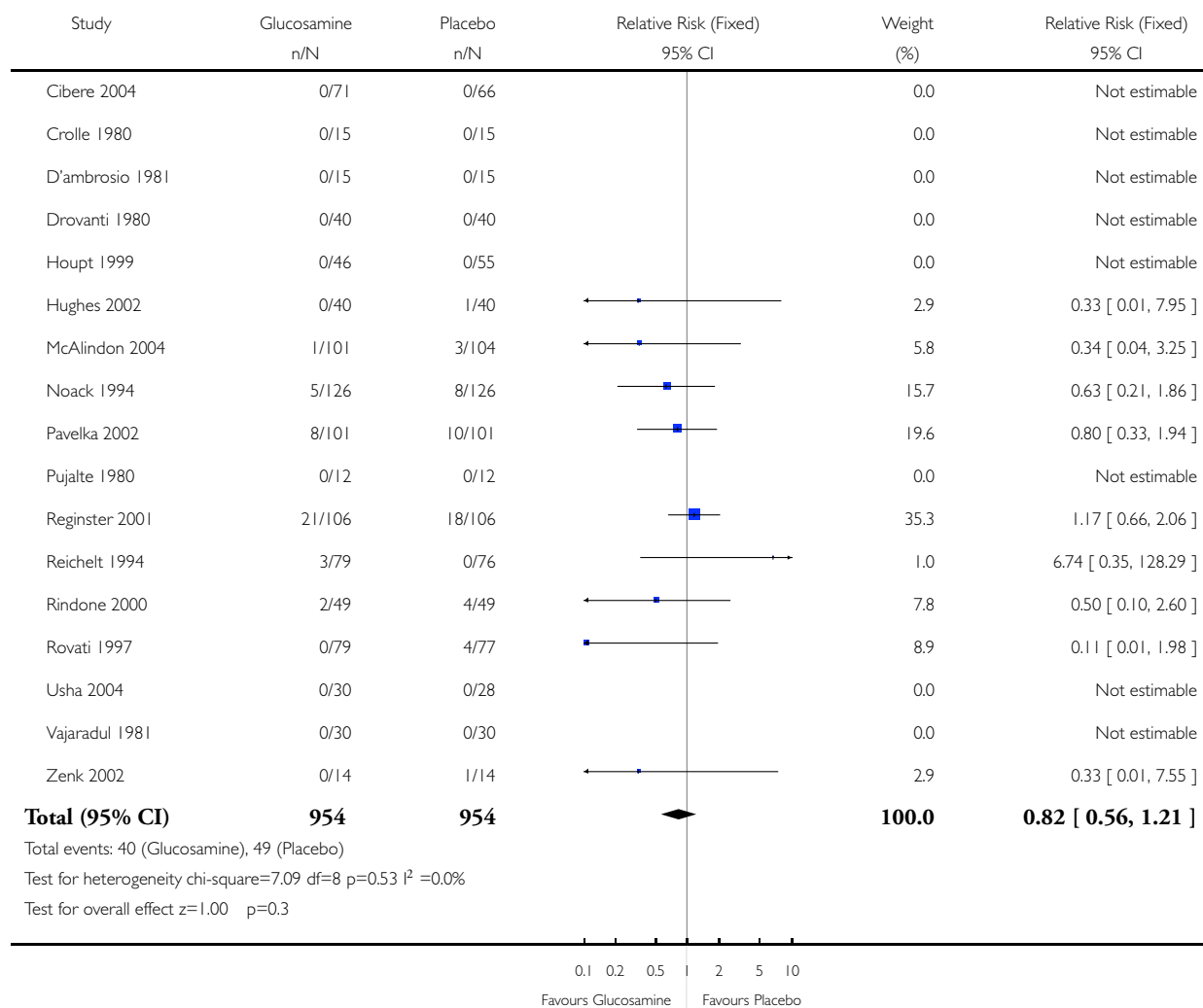


Analysis 01.12. Comparison 01 Glucosamine versus placebo, Outcome 12 Toxicity (Number of Withdrawals due to Adverse Events)

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 01 Glucosamine versus placebo

Outcome: 12 Toxicity (Number of Withdrawals due to Adverse Events)

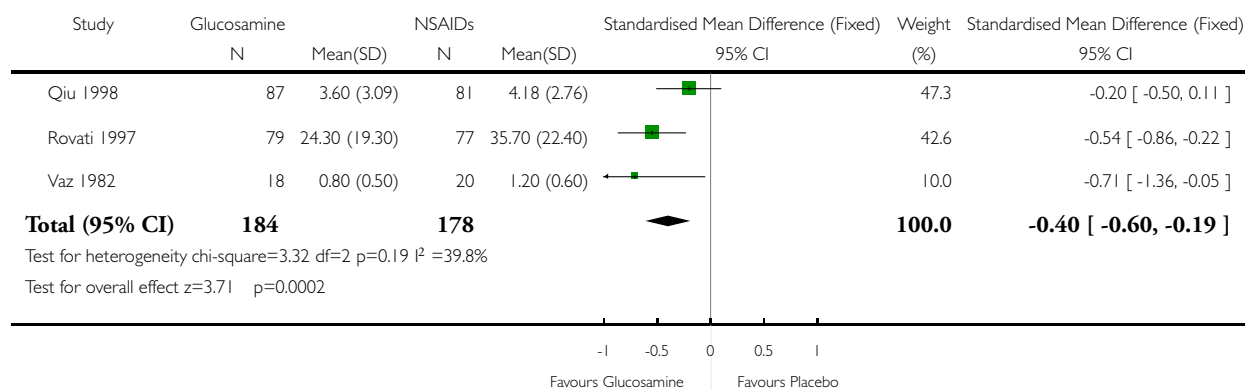


Analysis 02.01. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 01 Pain

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen]

Outcome: 01 Pain

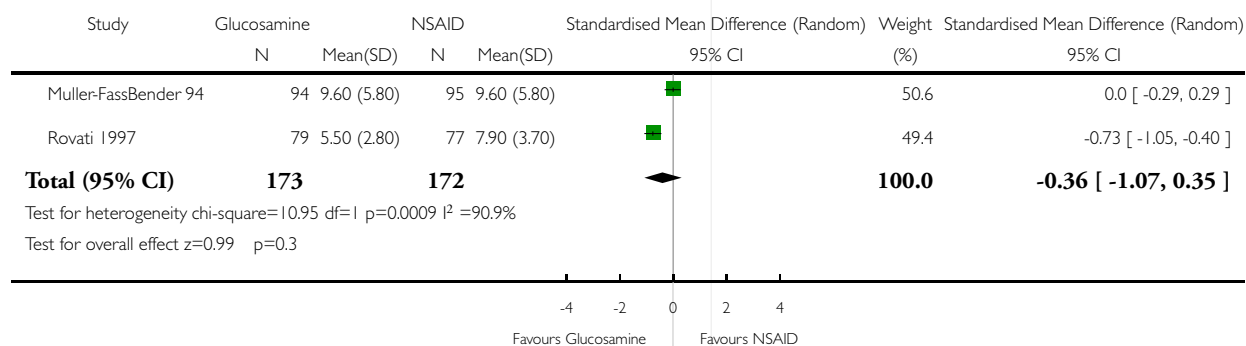


Analysis 02.02. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 02 Lequesne Index

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen]

Outcome: 02 Lequesne Index

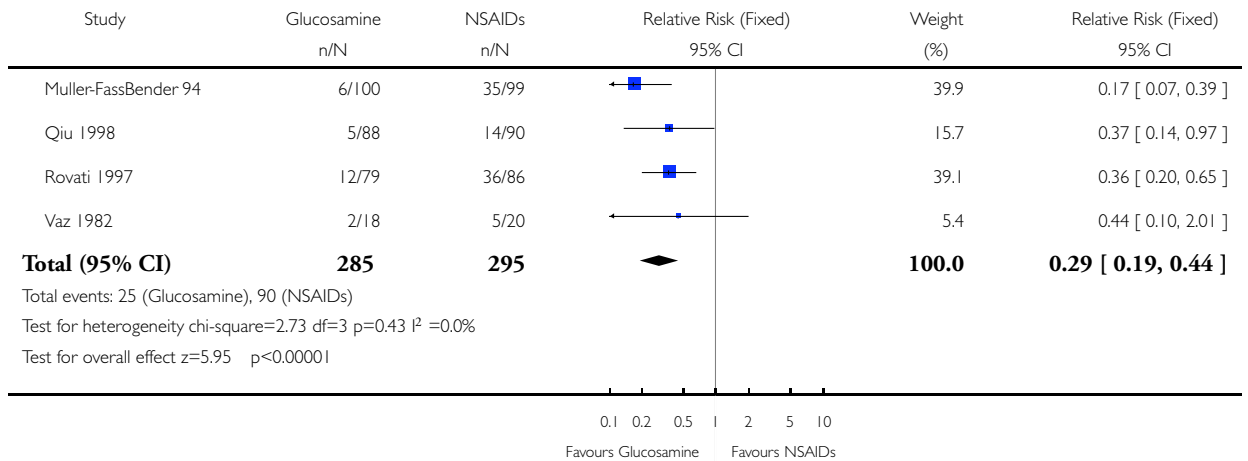


Analysis 02.03. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 03 Toxicity (Number of Patients Reporting Adverse Events)

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen]

Outcome: 03 Toxicity (Number of Patients Reporting Adverse Events)

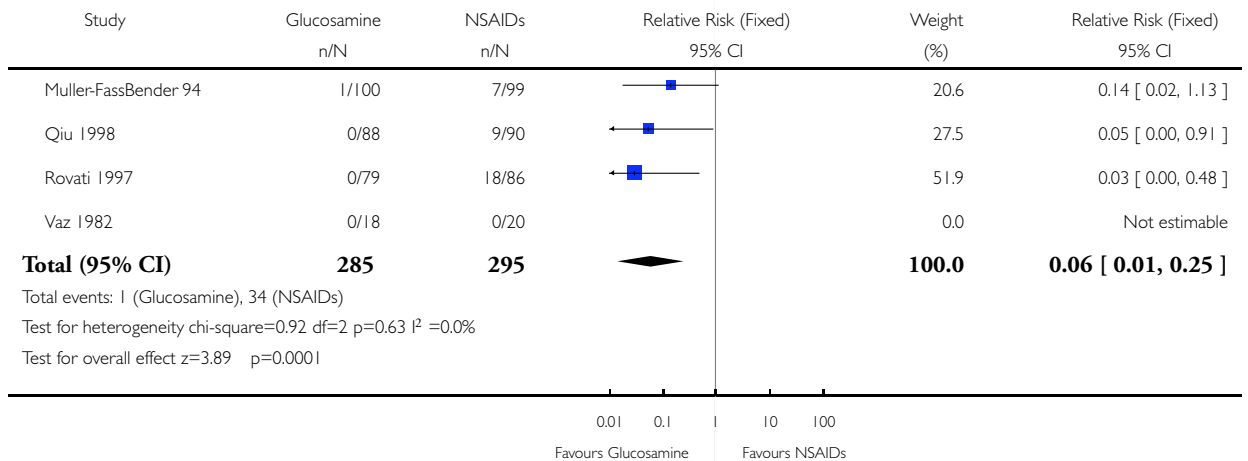


Analysis 02.04. Comparison 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen], Outcome 04 Toxicity (Number of Withdrawals due to Adverse Events)

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 02 Glucosamine versus NSAIDs [Piroxicam, Ibuprofen]

Outcome: 04 Toxicity (Number of Withdrawals due to Adverse Events)

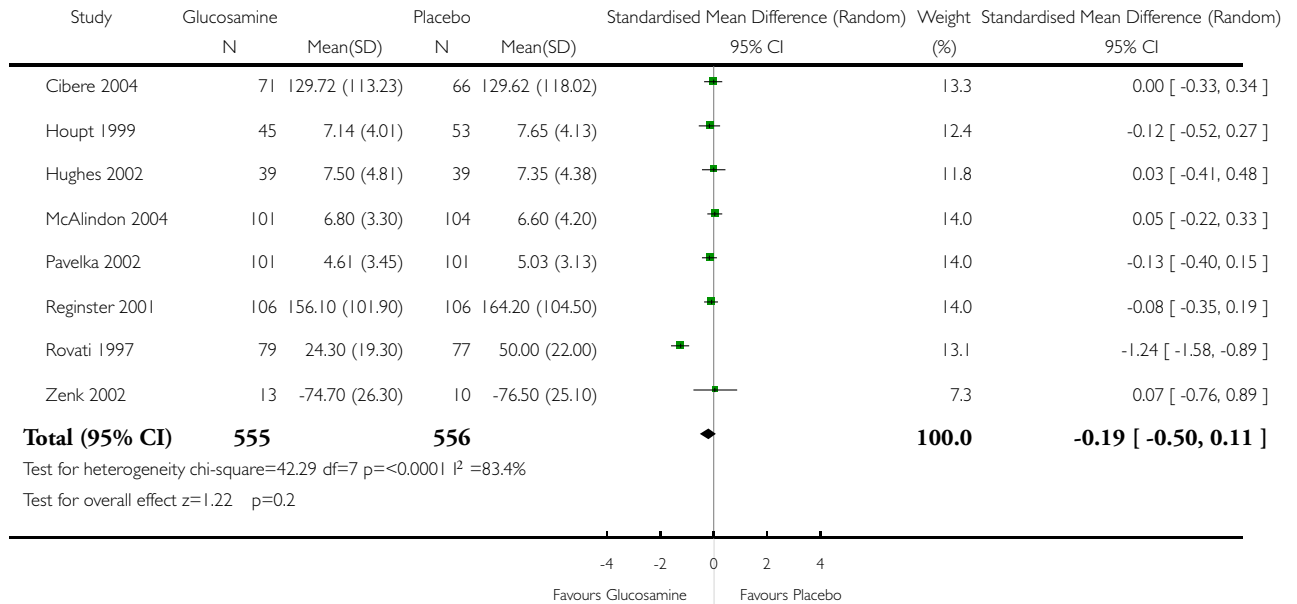


Analysis 03.01. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 01 Pain

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 01 Pain

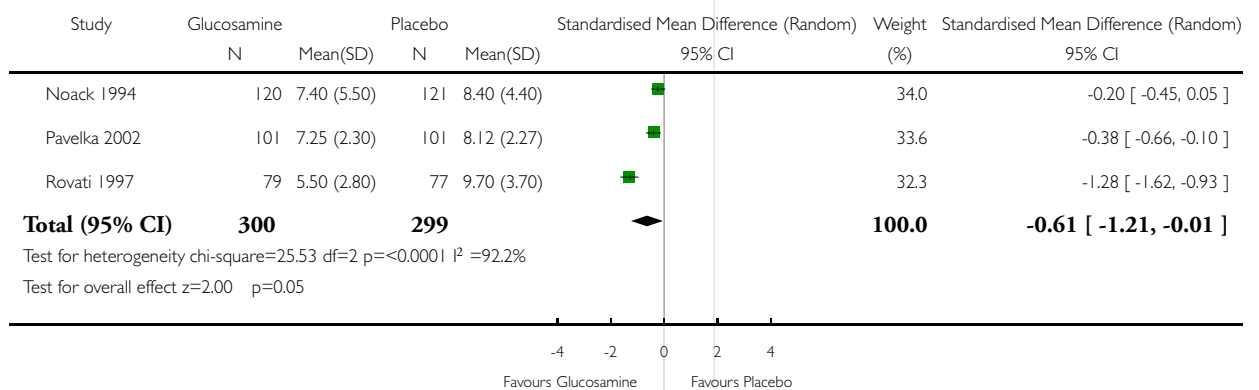


Analysis 03.02. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 02 Lequesne Index

Review: Glucosamine therapy for treating osteoarthritis

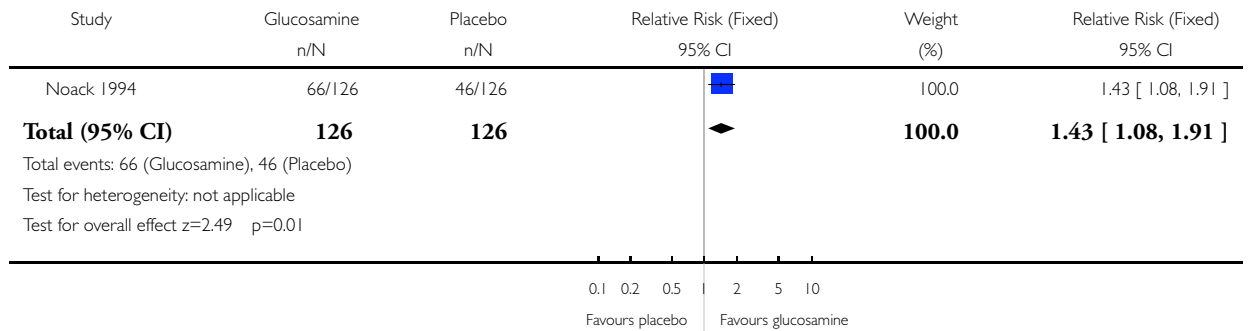
Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 02 Lequesne Index



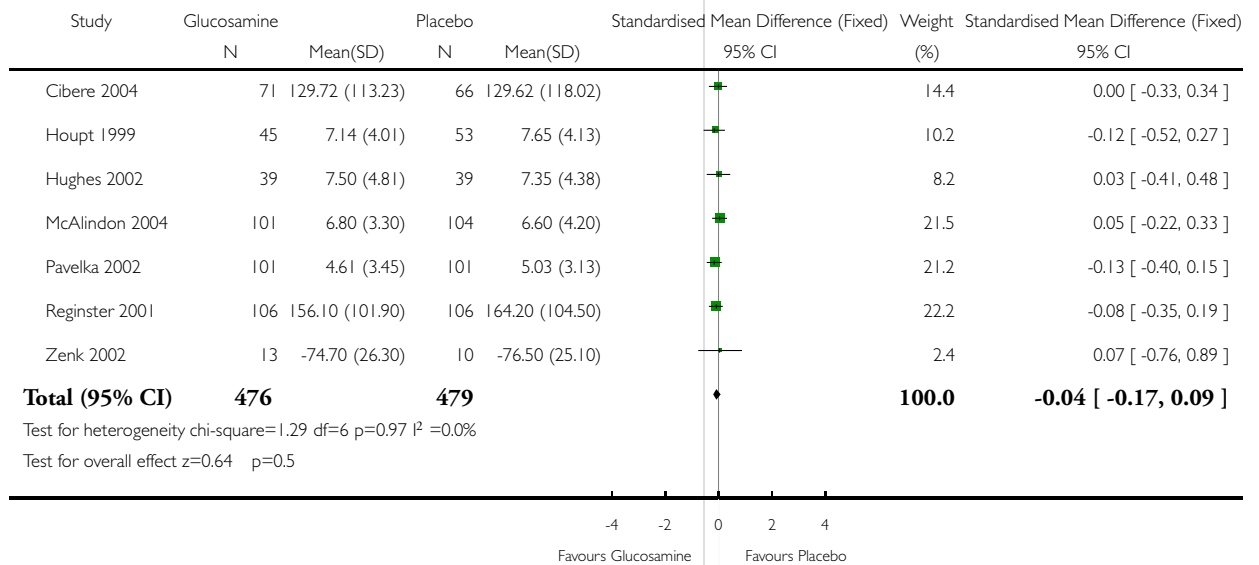
Analysis 03.03. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 03 Lequesne Index

Review: Glucosamine therapy for treating osteoarthritis
 Comparison: 03 Glucosamine versus placebo (Allocation concealment A)
 Outcome: 03 Lequesne Index



Analysis 03.04. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 04 WOMAC Pain Subscale

Review: Glucosamine therapy for treating osteoarthritis
 Comparison: 03 Glucosamine versus placebo (Allocation concealment A)
 Outcome: 04 WOMAC Pain Subscale

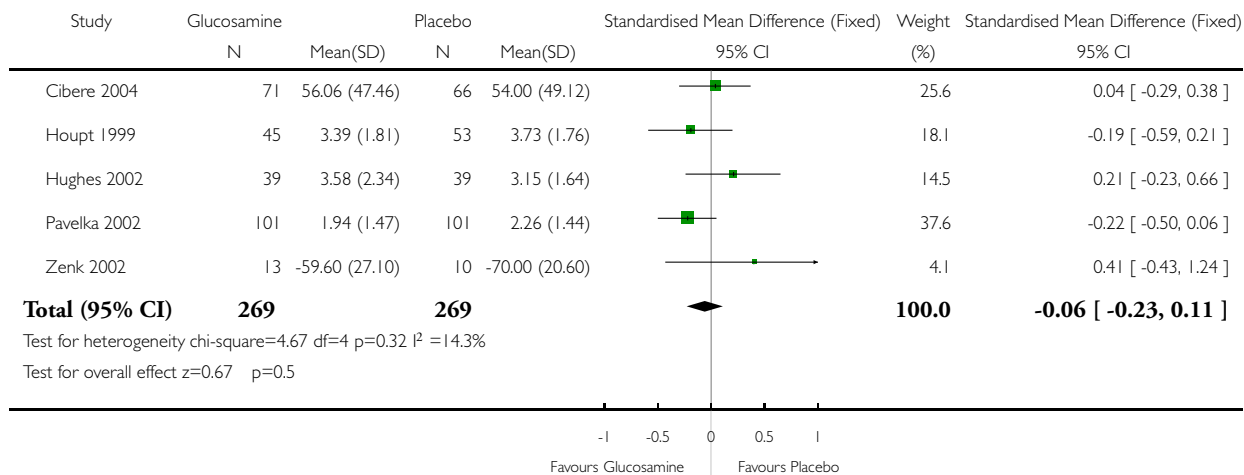


Analysis 03.05. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 05 WOMAC Stiffness Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 05 WOMAC Stiffness Subscale

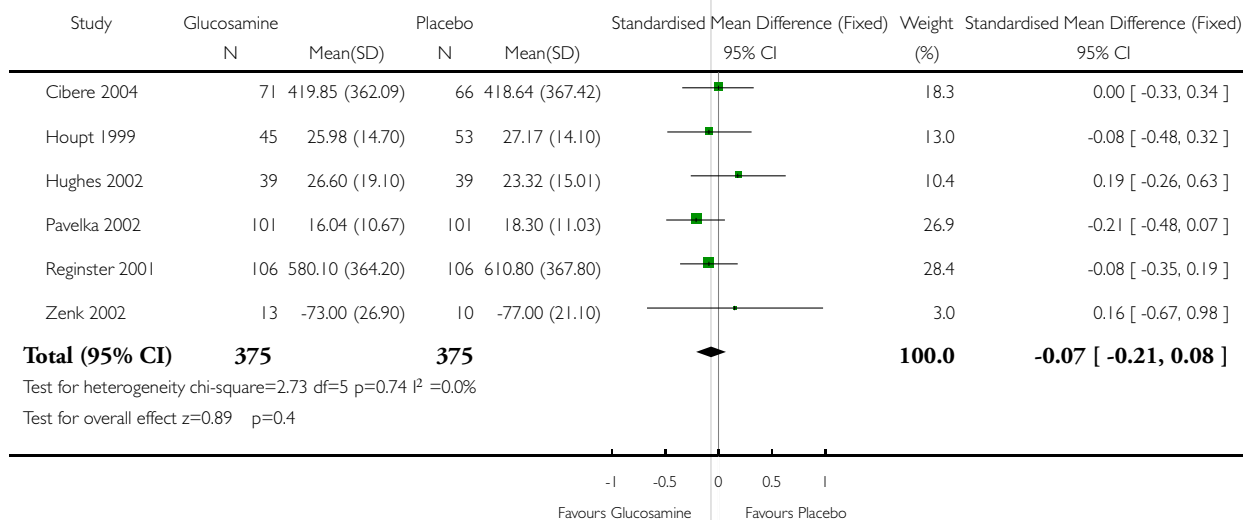


Analysis 03.06. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 06 WOMAC Function Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 06 WOMAC Function Subscale

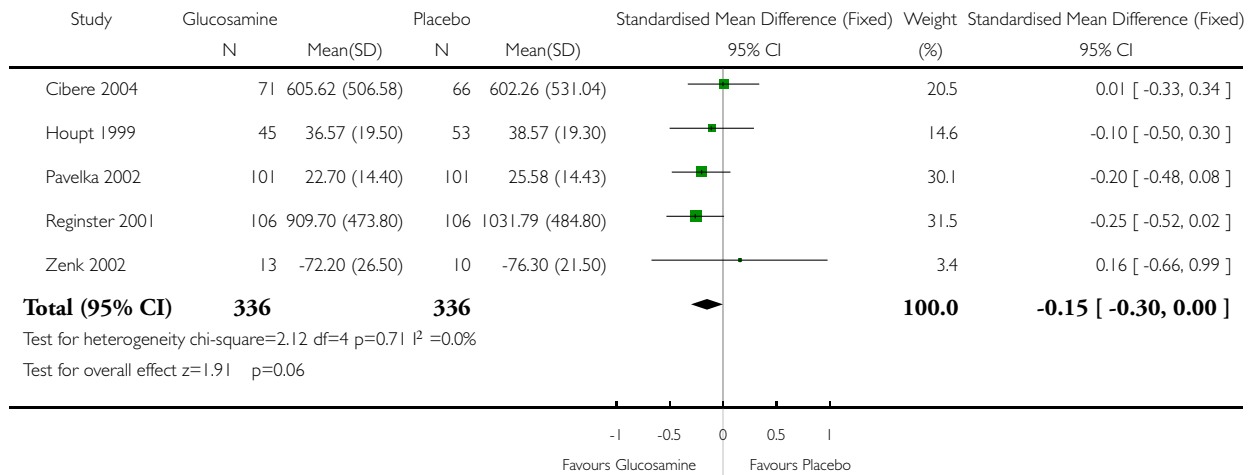


Analysis 03.07. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 07 WOMAC Total

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 07 WOMAC Total

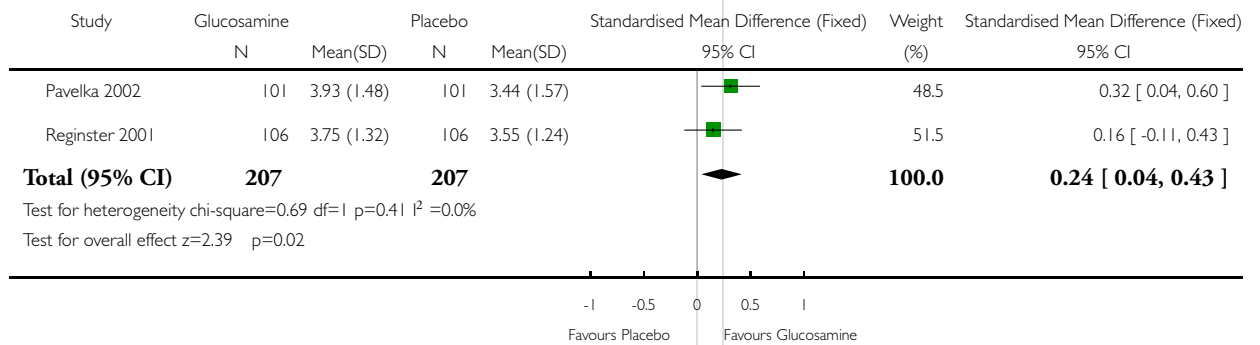


Analysis 03.09. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 09 Minimum Joint Space Width

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 09 Minimum Joint Space Width

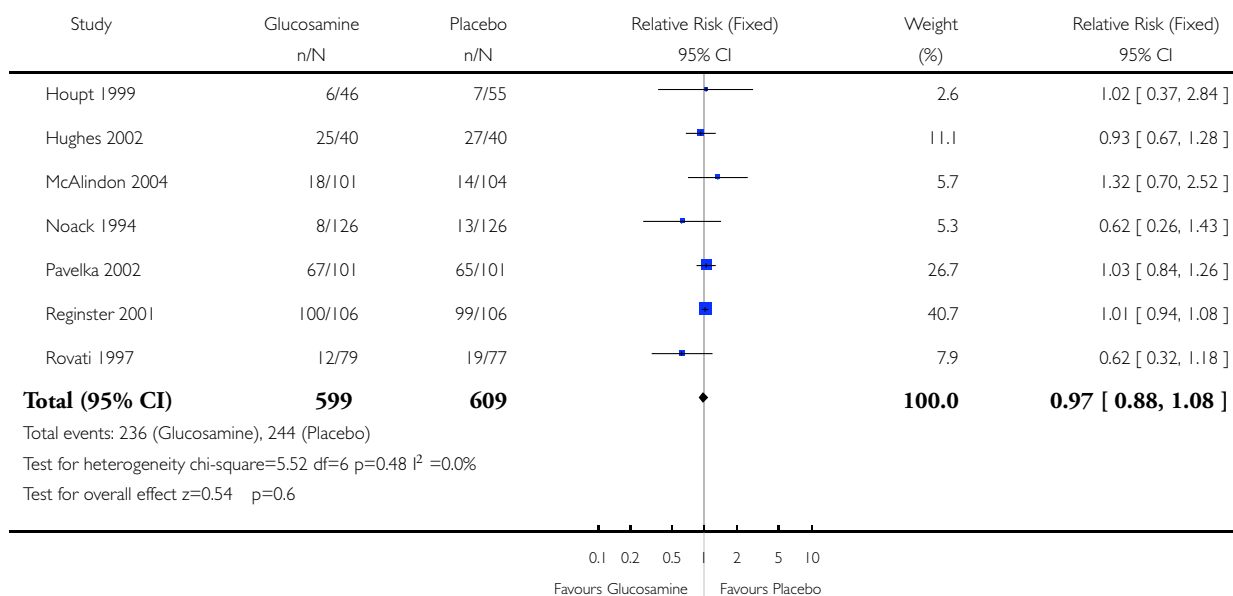


Analysis 03.11. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 11 Toxicity (Number of Patients Reporting Adverse Events)

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 11 Toxicity (Number of Patients Reporting Adverse Events)

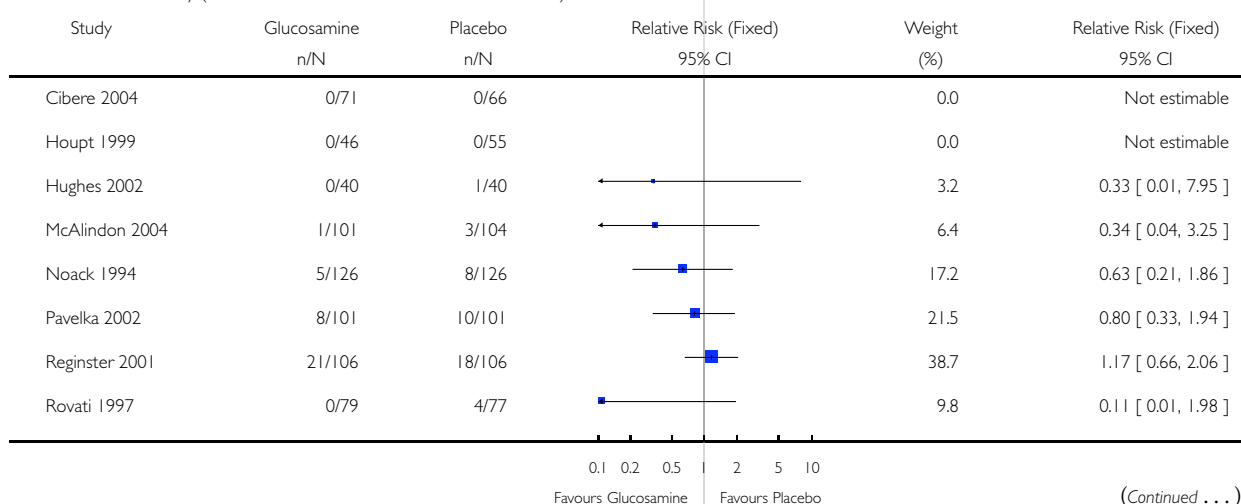


Analysis 03.12. Comparison 03 Glucosamine versus placebo (Allocation concealment A), Outcome 12 Toxicity (Number of Withdrawals due to Adverse Events)

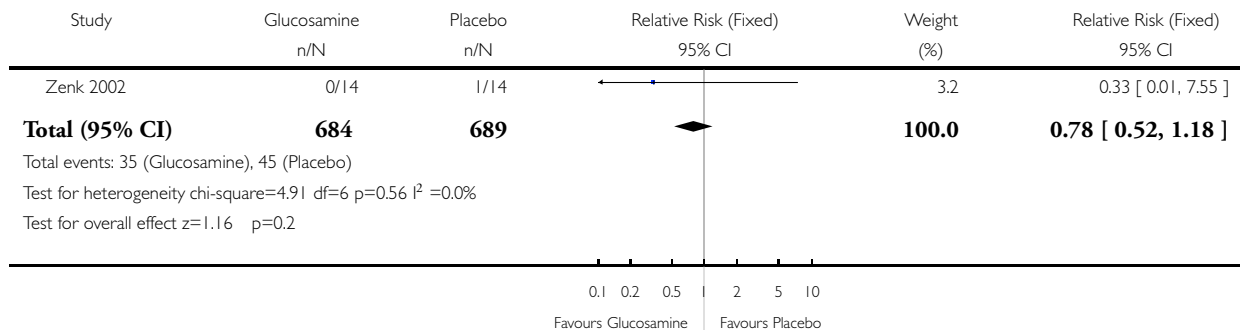
Review: Glucosamine therapy for treating osteoarthritis

Comparison: 03 Glucosamine versus placebo (Allocation concealment A)

Outcome: 12 Toxicity (Number of Withdrawals due to Adverse Events)



(... Continued)

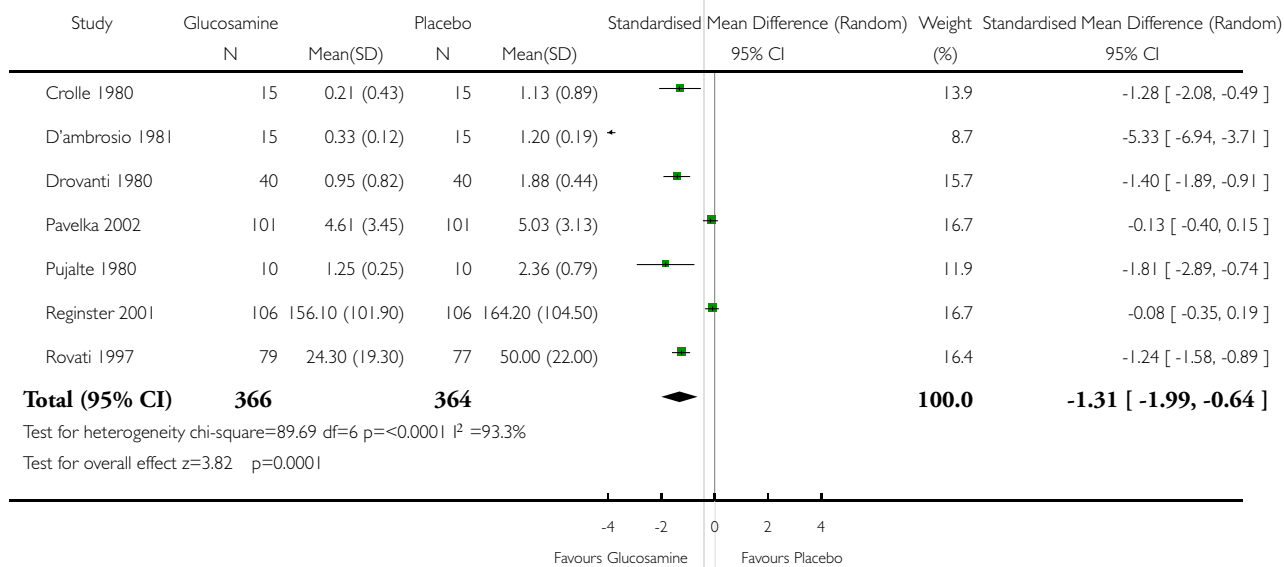


Analysis 04.01. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 01 Pain

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 04 Glucosamine versus placebo (Rotta preparation)

Outcome: 01 Pain

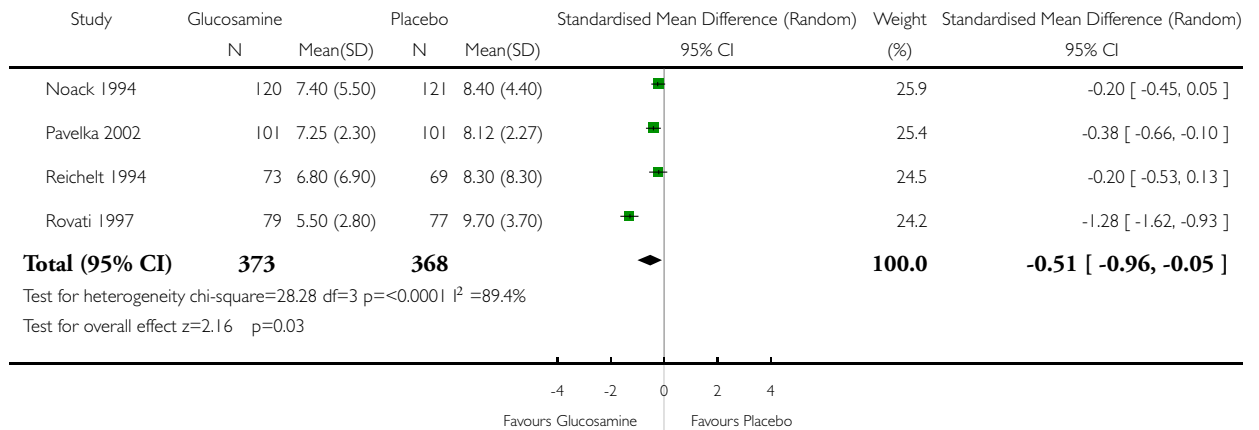


Analysis 04.02. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 02 Lequesne Index

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 04 Glucosamine versus placebo (Rotta preparation)

Outcome: 02 Lequesne Index

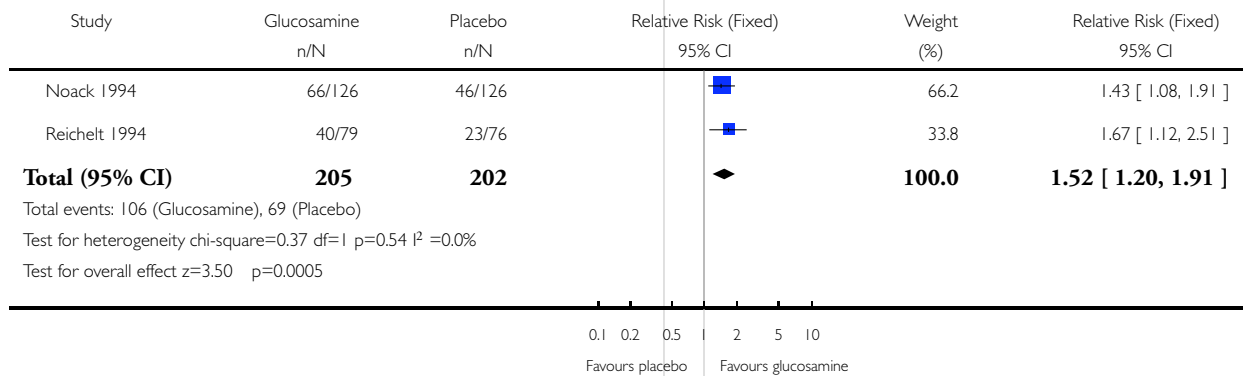


Analysis 04.03. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 03 Lequesne Index

Review: Glucosamine therapy for treating osteoarthritis

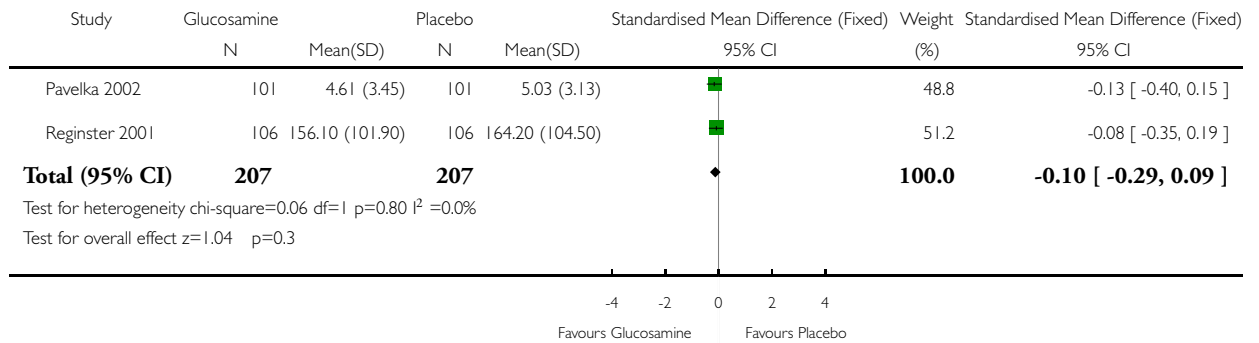
Comparison: 04 Glucosamine versus placebo (Rotta preparation)

Outcome: 03 Lequesne Index



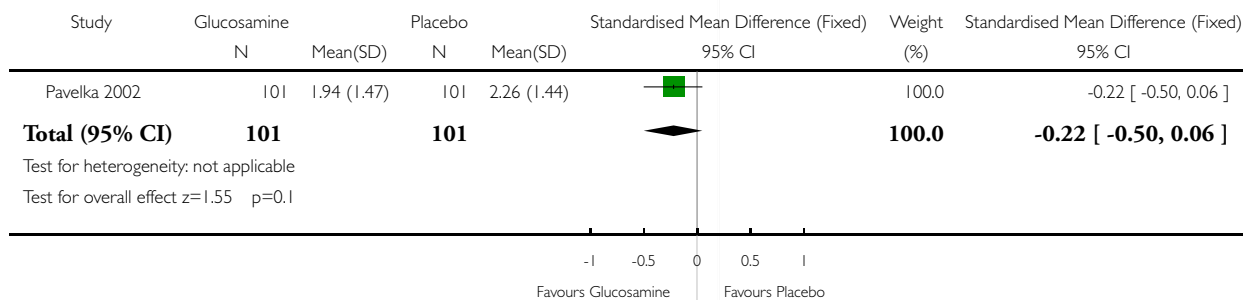
Analysis 04.04. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 04 WOMAC Pain Subscale

Review: Glucosamine therapy for treating osteoarthritis
 Comparison: 04 Glucosamine versus placebo (Rotta preparation)
 Outcome: 04 WOMAC Pain Subscale



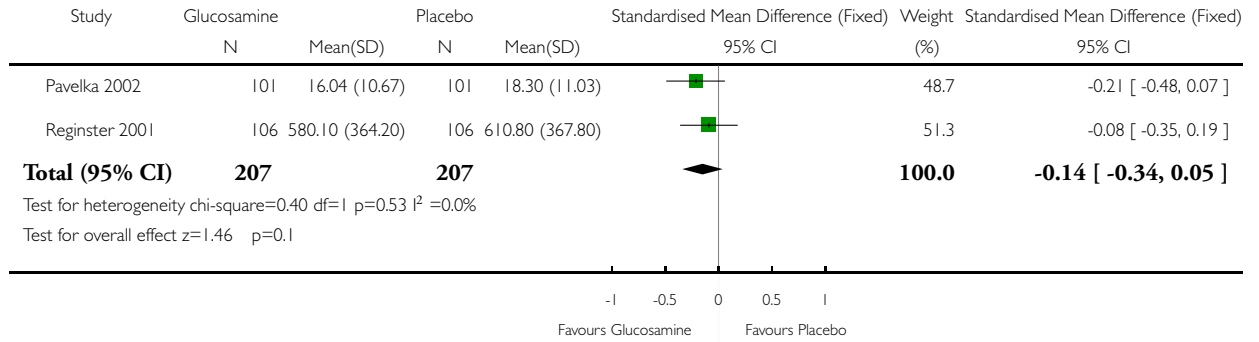
Analysis 04.05. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 05 WOMAC Stiffness Subscale

Review: Glucosamine therapy for treating osteoarthritis
 Comparison: 04 Glucosamine versus placebo (Rotta preparation)
 Outcome: 05 WOMAC Stiffness Subscale



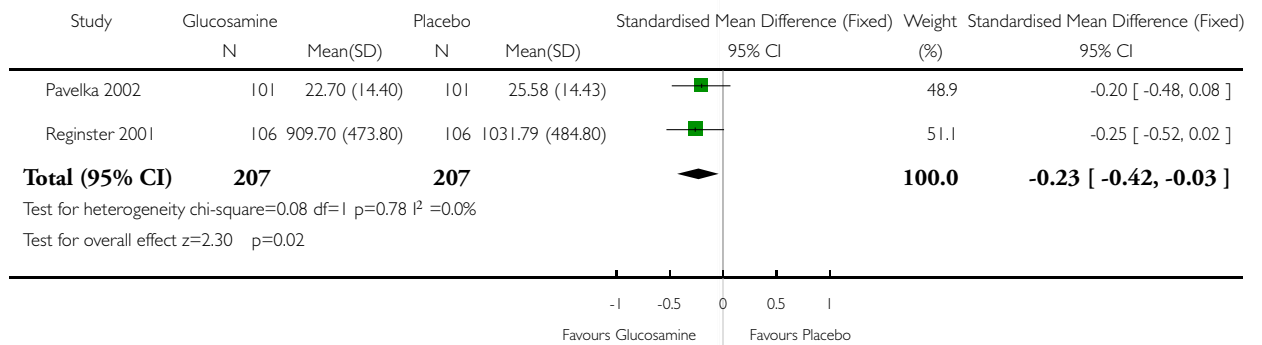
Analysis 04.06. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 06 WOMAC Function Subscale

Review: Glucosamine therapy for treating osteoarthritis
 Comparison: 04 Glucosamine versus placebo (Rotta preparation)
 Outcome: 06 WOMAC Function Subscale



Analysis 04.07. Comparison 04 Glucosamine versus placebo (Rotta preparation), Outcome 07 WOMAC Total

Review: Glucosamine therapy for treating osteoarthritis
 Comparison: 04 Glucosamine versus placebo (Rotta preparation)
 Outcome: 07 WOMAC Total

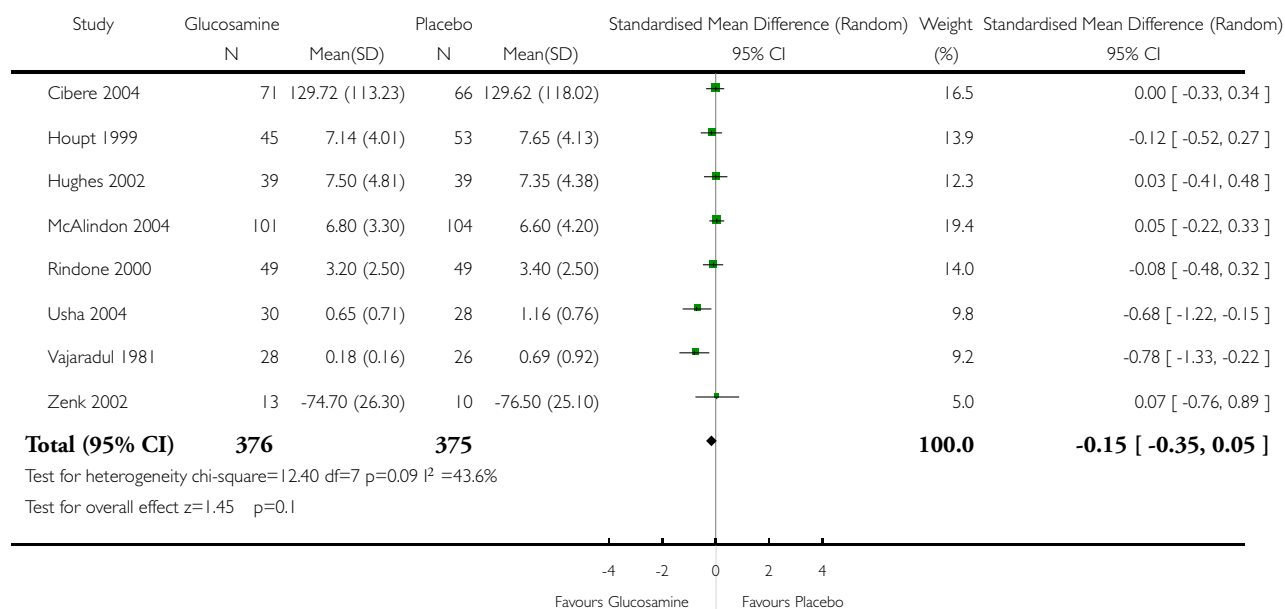


Analysis 05.01. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 01 Pain

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 05 Glucosamine versus placebo (non-Rotta preparation)

Outcome: 01 Pain

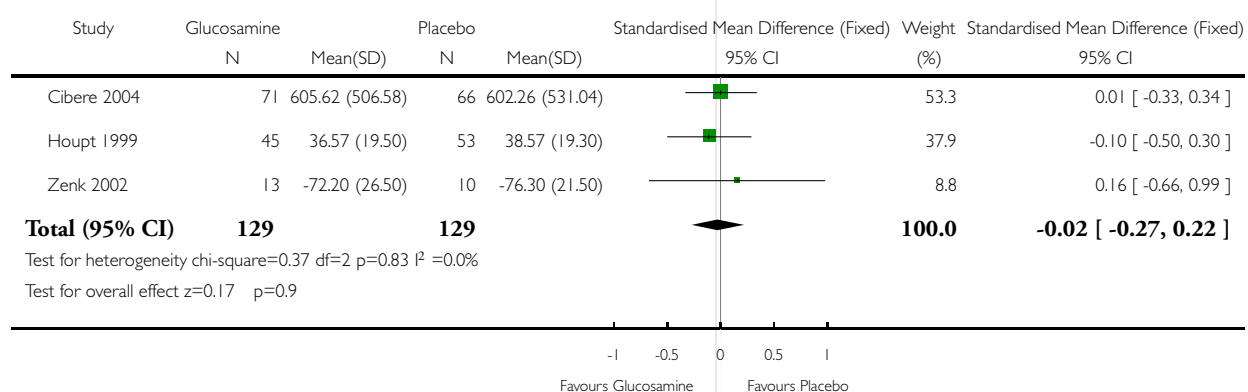


Analysis 05.02. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 02 WOMAC Total

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 05 Glucosamine versus placebo (non-Rotta preparation)

Outcome: 02 WOMAC Total

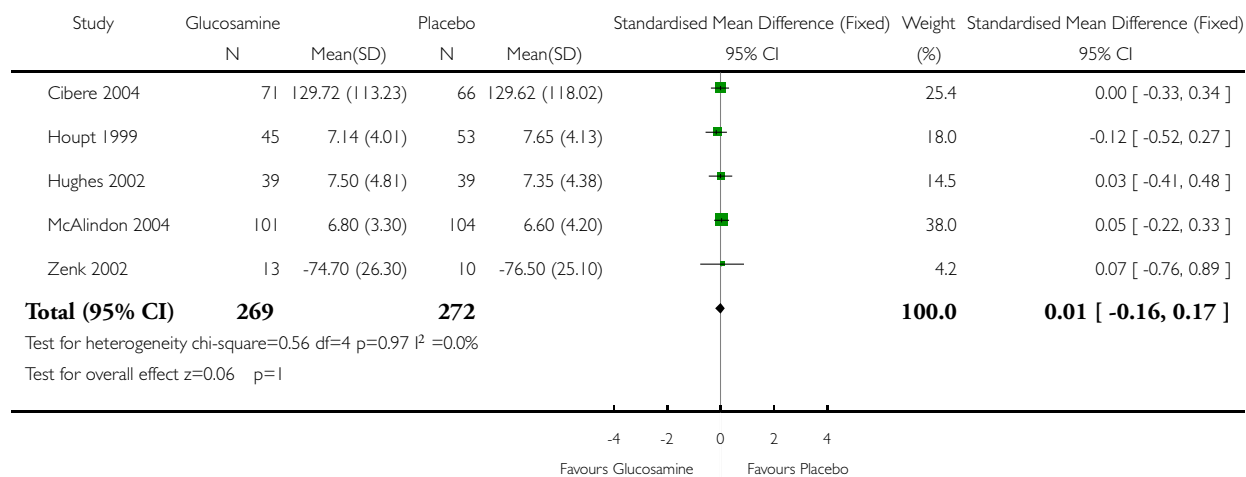


Analysis 05.04. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 04 WOMAC Pain Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 05 Glucosamine versus placebo (non-Rotta preparation)

Outcome: 04 WOMAC Pain Subscale

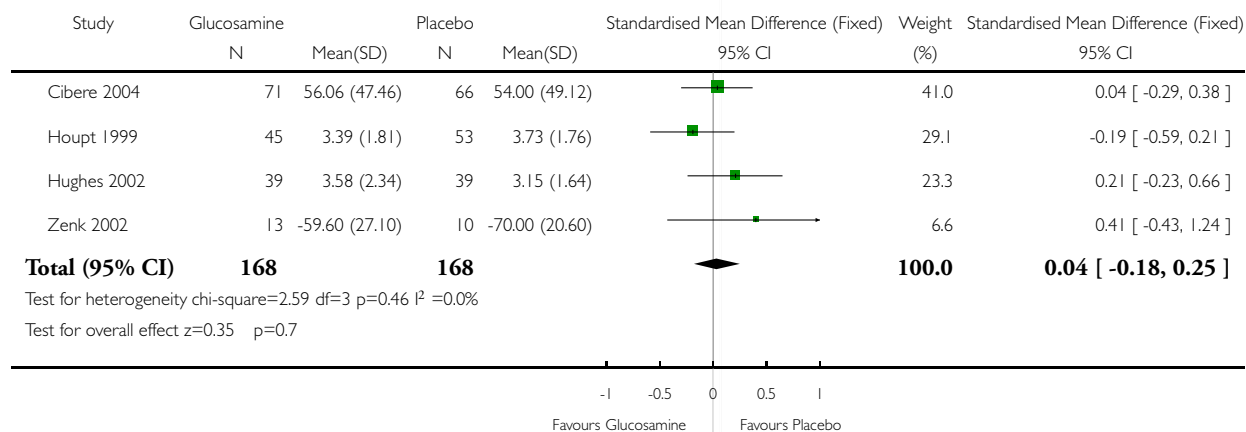


Analysis 05.05. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 05 WOMAC Stiffness Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 05 Glucosamine versus placebo (non-Rotta preparation)

Outcome: 05 WOMAC Stiffness Subscale



Analysis 05.06. Comparison 05 Glucosamine versus placebo (non-Rotta preparation), Outcome 06 WOMAC Function Subscale

Review: Glucosamine therapy for treating osteoarthritis

Comparison: 05 Glucosamine versus placebo (non-Rotta preparation)

Outcome: 06 WOMAC Function Subscale

