Glucosamine Effects in Humans: A Review of Effects on Glucose Metabolism, Side Effects, Safety Considerations, and Efficacy

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Glucosamine, 2-amino-2-deoxy-D-glucose, is an amino monosaccharide that is an essential component of mucopolysaccharides and chitin. Glycosaminoglycans, or mucopolysaccharides, are large complexes of negatively-charged carbohydrate chains that are incorporated into mucous secretions, connective tissue, skin, tendons, ligaments and cartilage. Glucosamine and its acetylated derivative, N-acetylglucosamine, are readily synthesized in the body from glucose. Because of its high concentration in joint tissues, the hypothesis that glucosamine supplements would provide symptomatic relief for osteoarthritis was developed more than 30 years ago.(1) Many clinical trials have tested this hypothesis(2) and glucosamine supplements are widely used to relieve arthritic complaints.(3)

To meet the demand for glucosamine nutritional supplements, three forms of glucosamine are commonly available: glucosamine hydrochloride, glucosamine sulfate, and N-acetyl-glucosamine. These glucosamine compounds are generally derived from chitin, a biopolymer present in the exoskeleton of marine invertebrate animals. The glucosamine derived from chitin in the cell walls of many fungi appears to be chemically identical to that found in marine invertebrates.(2)

Glucosamine directly enters into the hexosamine biosynthetic pathway. There is disagreement as to the presence of any undesired side effects of this exogenous glucosamine in animal systems.(site references if you believe necessary) Some, but not all, studies in animals suggest that glucosamine administration may produce insulin resistance and hyperglycemia by affecting insulin secretion and action.(2;4) However, most in vitro and animal studies have achieved blood and tissue levels 250 to 2500 times higher than would be expected with glucosamine doses used in humans.(4-7) Thus, it is important to rigorously review available data in humans to assess the effects of glucosamine intake on glucose homeostasis. Glucosamine is usually taken orally, as opposed to intra-arterially or intramuscularly, and 90% is absorbed.(8) Orally administered glucosamine has only 26% the bioavailability of intravenously administered glucosamine.(9) A significant fraction of orally administered glucosamine undergoes first-pass metabolism in the liver.(9) Blood levels achieved after oral glucosamine are only 20% those achieved with intravenous glucosamine.(2;8)

This review will examine the available data from humans to assess the effects of glucosamine on glucose metabolism. The effects of chronic glucosamine intake on blood chemistries, hematologic parameters, urinanalysis, occult blood in the feces, blood pressure and pulse rate will be tabulated. Side effects reported with glucosamine compared to placebo from placebo-controlled trials will be compared. Finally, an overview of the efficacy of glucosamine for arthritic complaints will be provided.

Materials and Methods

This review focuses on clinical studies performed with human subjects. The relevant articles were identified by Medline search and by review of articles referenced in primary reports and review articles. A previous review(2) and two meta-analyses(10;11) have performed detailed

literature searches. For this current review we reviewed the articles from these three previous reports and performed a Medline search for the years 2000-2003 using these key words: glucosamine and humans. We reviewed the references of all relevant articles for additional references. Articles included in this review relate to glucosamine administration to humans for investigational or therapeutic purposes. Appropriate articles were tabulated and the relevant data was extracted and tabulated. Semiquantitative and statistical analyses of data were performed.

The total number of patients represents the sum of all patients studied or the sum of all patients who had the specific measure described. Patient-years were calculated as follows:

Number of patients multiplied by number of study days divided by 365.

The ratio of side effects from glucosamine or placebo was calculated as follows:

Number of patients treated with glucosamine with side effects divided by number of patients treated with placebo with side effects.

The average ratio of side effects in each study for glucosamine and placebo was averaged, the standard error of these values calculated, and the 95% upper and lower confidence interval were calculated.

Significant differences were reported for 22 studies from patients with osteoarthritis. Since two meta-analyses(10;11) have carefully evaluated efficacy we tabulated reported outcomes and used simple arithmetic means and median values to characterize these reports. The P value reported represents the median of P values reported for each individual study since many studies had multiple P values reported. When significance difference was reported but the P value was not provided, a value of 0.05 was assigned. When values were not clinically significant, a value of 0.1 was assigned; this is justified because these studies reported favorable trends in efficacy or significant values for some outcome measures. The average P value is simply the average of reported P values. Five studies included comparisons of glucosamine to ibuprofen. These values are reported as percentages of patients who developed side effects in these two groups.

Results

Studies suitable for analysis

Thirty-five studies, including 32 studies of chronic glucosamine administration, were included in this analysis (Table 1). This includes data on 3073 patients treated with glucosamine for a total of 979 patient-years. Twenty-six chronic studies use a randomized, controlled trial (RCT) design, two were controlled studies and five studies were observational. Of the chronic studies, 29 used glucosamine alone, five included chondroitin sulfate and one included other supplements in the test preparation. Seven studies were comparator trials in which glucosamine was compared to other agents (ibuprofen in five studies, phenylbutazone in one study and piroxicam in one study). Of the 32 chronic studies, 28 used oral therapy exclusively, one used intramuscular administration alone, and three used oral administration in conjunction with intravenous, intramuscular, or intra-articular administration. The short-term studies were included to assess glucose metabolism. Four studies, one on skin wrinkles(12) and three on temporomandibular joint complaints(13-15) were included to make the safety assessment as comprehensive as possible.

Effects of glucosamine on glucose metabolism in humans

The reviewed studies are listed in Table 2. Four clinical trials reported fasting blood glucose values and mean values decreased nonsignificantly from 95.6 to 92.6 mg/dl. The

Reginster study enrolled 108 subjects and followed them for 3 years; they reported that blood glucose values were slightly lower.(16) Four other clinical trials indicated that there were no significant changes in clinical chemistry values implying no change in blood glucose values. One study(17) measured glycosylated hemoglobin (HbA1c) in 22 diabetic and 12 control subjects over 90 days. There were no significant changes in these values for diabetic or control subjects. In total, 9 studies assessed fasting glucose values and none reported deterioration of the blood glucose values. These 9 studies included 336 subjects treated for a total of 567 patient-years. For the entire group of 32 chronic studies of older subjects, three developed diabetes with placebo treatment and two developed diabetes with glucosamine treatment.

In two other studies (7;18) performed on metabolic research wards, large amounts of glucosamine-- ~7.2 grams or 9.7 grams of the glucosamine free base—were infused over 5 hours with no change in blood glucose values. These studies indicate that intake of glucosamine at recommended doses of 1500 mg or greater daily has essentially no effect on fasting blood glucose values in humans. These observations were reinforced by the recent report of Yu et al. (19) indicating that administration of 1500 mg glucosamine for 28 days had no effect on glucose tolerance or insulin sensitivity of 10 non-diabetic subjects.

Exposure to glucosamine in humans

Research volunteers or patients with arthritic complaints or skin conditions have received glucosamine for periods of 21-1095 days. The most common dose was 500 mg three times daily or 1500 mg/day. One group of 50 subjects received glucosamine hydrochloride at a dose of 3200 mg/day for 35 days. In terms of patient years (number of patients multiplied by duration of treatment), 3073 human volunteers or patients have received glucosamine for 979 patient-years. There have no serious or life-threatening effects reported.

In two metabolic ward studies, volunteers have received large doses of glucosamine intravenously over 300 minutes. Pouwels and colleagues(18) intravenously infused ~7.2 grams of glucosamine as the sulfate salt over a 300 minute period into 10 healthy volunteers. This was well tolerated and not associated with reported side effects. Monauni and colleagues(7) intravenously infused 9.7 grams of glucosamine over a 300 minute period into 10 healthy volunteers. Again this was well tolerated with no reported side effects. When they subsequently intravenously infused 30.5 grams of glucosamine (more than 20 times the usual daily dose) into 5 healthy volunteers, this dose was well tolerated by 4 subjects and only one had symptoms—he developed a headache. These amounts (7.2 grams, 9.7 grams, and 30.5 grams) were of the free-base glucosamine.

These studies indicate that glucosamine is well tolerated by healthy volunteer subjects at very high doses. Individuals with degenerative joint disease also tolerate 1500-3200 mg/day for periods of 3 years. Thus, 3200 mg/day or 49 mg/kg/day has been tolerated by older subjects for periods of 35 days. Because the blood level achieved with intravenous glucosamine is approximately five-fold higher than with oral administration,(8) it appears that humans can easily tolerate more than 9.7 grams/day. In calculating the acceptable daily intake (ADI) of glucosamine, these calculations were used. Humans tolerate more than 9.7 grams of free-base glucosamine. These young men have average weights of ~ 70 kg. The calculation of mg/kg is as follows: 9700 mg divided by 70 kg equals more than 138 mg/kg/day of the free base glucosamine. Because glucosamine hydrochloride provides 83% free base, humans tolerate more than 166 mg/kg/day (138 divided by 0.83) of glucosamine hydrochloride. Furthermore, since only 90% of glucosamine is absorbed,(20) humans tolerate more than 184 mg/kg/day (166

divided by 0.9) of the glucosamine hydrochloride. Thus, 184 mg/kg/day is a conservative recommendation for an acceptable daily intake (ADI) of glucosamine hydrochloride.

Objective measures of safety

Thirteen studies reported specific safety measures including some of these assessments: chemistry panel including liver and kidney safety assessments, hematologic parameters (white blood count, red blood count, hemoglobin, and platelet count), urinalyses, occult blood measurements of stool, and cardiovascular parameters including blood pressure and pulse rate (Table 2). None of the studies reported adverse effects on these measurements from glucosamine administration. In general these safety reports included about 700 subjects representing approximately 600 patient-years. Specifically the number of studies assessing various parameters were as follows: chemistry panel, 11; hematologic parameters, 13; urinalyses, 10; occult blood, 3; and cardiovascular parameters, 6. Blood pressure and pulse rate were monitored continuously for the 21 subjects who had large amounts of glucosamine infused intravenously with no reported adverse effects.(7;18) None of the studies reported significant changes in these parameters.

Common symptoms with placebo or glucosamine

Nonspecific symptoms are commonly reported in clinical trials. In a 3-year study, 93% of subjects receiving placebo reported symptoms.(16) The most common symptoms reported with placebo or glucosamine were these: mild gastrointestinal symptoms including constipation, diarrhea, nausea, dyspepsia, excessive gas, abdominal distension, and abdominal cramps; headache; and skin rash or pruritis. Eighteen chronic studies that provided side effect data comparing glucosamine to placebo were analyzed. These studies, as summarized in Table 2, included 988 subjects and 706 patient-years of observation. In 13 of the 18 studies, symptoms were reported less commonly in glucosamine-treated subjects than in placebo-treated subjects. The ratio of symptoms for glucosamine compared to those for placebo is presented for each study. The placebo has a score of 1.0 and the frequency of symptoms with glucosamine is a fraction of this. When the frequency of symptoms is the same the ratio for glucosamine is 1.0. When less symptoms are reported for glucosamine that placebo, the ratio is less than 1.0. Only two studies reported that symptoms were more common with glucosamine than placebo. The frequency of symptoms with glucosamine ranged from none (0.0) to 143% (1.43) of those reported for placebo. The average for the ratio of symptoms for glucosamine compared to placebo was 0.76 (95% confidence interval, 0.61 to 0.92). This suggests that symptoms were 24% less common with glucosamine than placebo and that this was statistically significant. Richy and colleagues,(11) in their meta-analysis, indicated that the adverse effect rate with glucosamine was 80% of that for placebo.

The Institute of Medicine report(2) summarizes case reports and other adverse events occurring with glucosamine use. This report concludes that: “Human studies show an equal incidence of mild, transient adverse effects in placebo control groups and glucosamine groups.”(2)

Five studies compared side effects of glucosamine with ibuprofen, the most commonly used non-steroidal anti-inflammatory agent for arthritis. The prevalence of side effects in patients using glucosamine was 10.0% compared to 32.5% for patients using ibuprofen. The Institute of Medicine report also concluded that side effects were less common with glucosamine than with ibuprofen.(2)

Efficacy assessment

The efficacy of glucosamine for arthritic complaints has been extensively studied and two recent meta-analyses(10;11) are available. McAlindon and colleagues(10) conclude that glucosamine was moderately efficacious for relief of arthritic complaints. Richy and colleagues(11) conclude that glucosamine had highly significant efficacy on all aspects of knee osteoarthritis including joint space narrowing, pain, and mobility scores. Twenty-two clinical studies of patients with osteoporosis were reviewed (Table 3); this does not include the three studies of TMJ symptoms. Twelve studies reported significant differences and included P values (from 0.05 to 0.001). Seven indicated that significant improvement was seen but did not provide P values; a P value of 0.05 was assigned to these studies. Only three studies indicated that no significant difference was seen and two noted a slight improvement with glucosamine administration; a P value of 0.1 was assigned to these studies since they reported favorable but not quite statistically significant results. The average of all reported and imputed P values for the 22 studies was 0.040 and the median P value was 0.05. While a detailed analysis of efficacy was not undertaken, this survey indicates that glucosamine administration, at a dose of 1500 mg/day, is moderately effective in decreasing arthritic complaints.

Discussion

Glucosamine has been extensively studied in animals and humans. We reviewed data from 32 clinical trials including 3073 individuals treated with glucosamine for periods of 21-1095 days (979 patient-years). Like the Institute of Medicine review,(2) we conclude that mild, transient side effects are seen in placebo and glucosamine treated individuals. Our analysis of side effects suggests that side effects are about 24% less frequent in glucosamine-treated individuals than in placebo-treated individuals; Richy et al.(11) calculated that side effects are 20% less common in glucosamine-treated subjects than in the placebo groups. Our analysis and that of the Institute of Medicine(2) indicate that side effects from glucosamine are substantially lower than from ibuprofen, a widely uses non-steroidal anti-inflammatory drug.

The effects of glucosamine on glucose metabolism have interested laboratory investigators for many years because pharmacologic concentrations of glucosamine affect insulin action and secretion. Glucosamine is a common metabolic product in most tissues of the body and is incorporated into glycosaminoglycans.(8) Setnikar and Rovati(8) have reviewed the metabolism of glucosamine in humans and these data can be summarized. Glucosamine sulfate or hydrochloride salts are dissociated in the stomach and free glucosamine enters the small intestine where 90% is absorbed. Much of the glucosamine is metabolized in the first pass through the liver. The blood level of glucosamine after oral administration approximates 20% of that observed with intravenous administration. Glucosamine is taken up by cells by glucose transporter proteins but the affinity of glucosamine for these transporters is substantially lower than that of glucose.(5) Thus, it seems likely that the concentration of glucosamine in most cells would be substantially lower than that in plasma. With intravenous administration of 9.7 grams over 5 hours, serum glucosamine concentrations of 0.7 mmol/l were achieved.(7) With administration of 500 mg in three divided doses it seems unlikely that serum concentrations above 0.01 mmol/l would be achieved. In vitro studies that show effects of glucosamine on glucose metabolism have used concentrations of 2.5 to 50 mmol/l.(5;6;21) The effective dose for a 50% change (ED_{50}) in insulin-stimulated glucose uptake in isolated fat cells is 25-30 mmol/l(6) or ~2500 times the tissue level likely to be achieved with oral administration of glucosamine in

humans. Thus, it seems very unlikely that oral administration of 1500 mg/d (the commonly used amount) to 3200 mg/d (an amount used in one chronic study) of glucosamine would have a discernable effect on metabolic pathways involved in glucose metabolism in humans.

Because of the effects of large concentrations of glucosamine on glucose metabolism in animal and in vitro models we rigorously examined the available data related to this question in humans. In clinical trials there is no evidence that glucosamine in usual doses affects fasting plasma glucose concentrations. In one clinical trial(19) glucosamine administration had no effect on estimates of insulin sensitivity. Finally, when large amounts of glucosamine (7.2 or 9.7 grams) was infused into healthy volunteers, no adverse effects on blood glucose concentrations were observed over the 5-hour period of study.(7;18) These observations indicate that 9.7 grams of glucosamine, as free base, or 138.6 mg/kg are well tolerated. Since glucosamine hydrochloride provides 83% free base, the tolerated dose would be 167.0 mg/kg. Since only 90% of glucosamine is absorbed(8), the tolerated dose would increase to 186 mg/kg. This a conservative estimate of the acceptable daily intake (ADI). If one uses the blood level after oral administration to be 20% of that after intravenous administration,(2;8) one could calculate that the tolerable dose of free base glucosamine would be 693 mg/kg (i.e., 138.6 divided by 0.2). Thus, we conclude that 186 mg/kg is a conservative estimate of the ADI for glucosamine hydrochloride.

In reviewing these clinical trials we tabulated data on efficacy of glucosamine administration on symptoms of osteoarthritis. Our observations are consistent with the rigorous meta-analyses of McAlindon et al.(7) and Richy et al.(10;11) Individuals with osteoarthritis of the knee or spine have significantly less symptoms while taking glucosamine that those taking placebo. McAlindon et al.(10) conclude that glucosamine is moderately efficacious for relief of symptoms of osteoarthritis. Richy et al.(11) conclude that glucosamine has highly significant effects on all aspects of knee osteoarthritis. The effects of glucosamine sulfate compared to glucosamine hydrochloride have not been examined in a comparator trial. Because of the disassociation of the salt in the stomach, it seems unlikely that the two preparations would have differing effects. Comparing side effects and reports of efficacy across trials suggests that the two glucosamine salts have similar effects.

Conclusions

Results from 32 clinical trials with glucosamine were reviewed. These trials included 3073 subjects studied for 979 patient-years. While there have been concerns originating from some animal studies that glucosamine might adversely affect glucose metabolism, careful studies in humans show not adverse effects on glucose homeostasis. Overall, 9 studies including 336 subjects for 567 patient-years reported no adverse effects on glucose metabolism. Glucosamine is well tolerated by humans for periods of up to three years. While the usual dose is 1500 mg/day in three doses, doses of up to 3200 mg/day were well tolerated. Healthy young subjects had no adverse effects from infusion of 9.7 grams and only one of five developed a headache when 30.5 grams was infused. This suggests that an acceptable daily intake for glucosamine hydrochloride (ADI) is higher than 186 mg/kg/day. In 13 clinical trials reporting safety information there were no adverse effects of glucosamine on blood chemistries, hematologic parameters, urinalysis, occult blood in feces, or cardiovascular parameters. Symptoms or side effects were reported significantly less frequently with glucosamine than with placebo. Reported side effects were 24% less common in subjects treated with glucosamine than with placebo. Finally, glucosamine appears to be moderately to highly effective in decreasing symptoms resulting from osteoarthritis.

Table 1. Studies evaluated.

Study	Type Study	Glucosamine form	Other Treatment	Route*	Dose mg/d	No.of subjects	Duration days	Patient-Years
Almada (22)	RCT	SO4	None	Oral	1500	6	84	1.4
Braham (23)	RCT	HCl	None	Oral	2000	25	84	5.8
D'Ambrosio (1)	RCT	SO4	None	oral/iv/im	1500	15	21	0.9
Das (24)	RCT	HCl	CHS	Oral	2000	46	192	24.2
Drovanti (25)	RCT	SO4	None	Oral	1500	40	30	3.3
Forster (26)	RCT	SO4	None	Oral	1500	78	90	19.2
Giordano (27)	Observational	SO4	None	Oral	1500	20	365	20.0
Houpt (3)	RCT	HCl	None	Oral	1500	45	147	18.1
Hughes (28)	RCT	SO4	None	Oral	1500	39	168	18.0
Leffler (29)	RCT	HCl	CHS, Mn	Oral	1500	31	112	9.5
Monauni: First(7)	Controlled	uncertain	None	Iv	9.7g	10	300"	0.0
Second study (7)	Controlled	uncertain	None	Iv	30.5 g	5	300"	0.0
Muller-Fa□bender (30)	RCT-C	SO4	Vs. ibuprofen	Oral	1500	100	28	7.7
Mund-Hoym (31)	Controlled	SO4	vs phenylbutazone	oral/im	1000	40	32	3.5
Murad(12)	Controlled	SO4	Supplement	Oral	uncert	57	35	5.5
Nguyen (13)	RCT	HCl	CHS	Oral	1500	19	84	4.4
Noack (32)	RCT	SO4	None	Oral	1500	120	28	9.2
Pavelka (33)	RCT	SO4	None	Oral	1500	84	1095	252.0
Pouwels (18)	Controlled	SO4	None	Iv	~7.2g	6	300"	0.0
Pujalte (34)	RCT	SO4	None	Oral	1500	11	49	1.5
Qiu (35)	RCT-C	SO4	vs ibuprofen	Oral	1500	88	28	6.8
Reicheit (36)	RCT	SO4	None	IM	114	73	42	8.4
Reginster (16)	RCT	SO4	None	Oral	1500	87	1095	261.0
Rindone (37)	RCT	SO4	None	Oral	1500	49	60	8.1
Rovati (38)	RCT-P-C	SO4	vs piroxicam	Oral	1500	80	150	32.9
Rovati 1 (39)	RCT	SO4	None	Oral	1500	123	28	9.4
Second study (39)	RCT	SO4	None	Oral	1500	76	42	8.7
Third study (39)	RCT-C	SO4	vs ibuprofen	Oral	1500	100	28	7.7
Scroggie (17)	RCT	HCl	CHS	Oral	1500	22	90	5.4
Shankland (14)	Observational	HCl	CHS	Oral	3200	50	35	4.8
Tapadinhas (40)	Observational	SO4	None	oral	1500	1367	50	187.3
Thie (15)	RCT-C	SO4	vs ibuprofen	oral	1500	22	90	5.4
Yu (19)	Observational	SO4	None	oral	1500	12	28	0.9
Vajranetra (41)	Observational	SO4	None	oral/ia	1500	108	84	24.9
Vas (42)	RCT-C	SO4	vs ibuprofen	oral	1500	19	56	2.9
Sum						3073		979

* Abbreviations: RCT- randomized controlled trial; C, comparator; P, placebo; CHS, chondrotin sulfate; iv, intravenous; im, intramuscular; ia, intraarticular.

Table 2. Evaluation of fasting plasma glucose and safety parameters.

Study	Glucose before	mg/dl after	Sum-mary	Blood chem	CBC	UA	Occult blood	BP P	Side Effects GluN/P
Almada (22)	94	94		NA	NA	NA	NA	NA	NA
Braham (23)	NA			NA	NA	NA	NA	NA	1.10
D'Ambrosio (1)	109	97		NSC	NSC	NSC	NA	NSC	1.00
Das (24)	NA			NA	NA	NA	NA	NA	0.89
Drovanti (25)	82	82		NSC	NSC	NA	NSC	NA	0.83
Forster (26)	NA			NA	NA	NA	NA	NA	0.20
Giordano (27)	NSC			NSC	NSC	NSC	NA	NA	1.00
Houpt (3)	NA			NA	NA	NA	NA	NA	1.00
Hughes (28)	NSC			NSC	NSC	NSC	NA	NA	0.90
Leffler (29)	NA			NA	NSC	NA	NSC	NSC	0.97
Monauni 1 (7)	NSC			NA	NA	NA	NA	NSC**	NA
Second study (7)	minimal effect			NA	NA	NA	NA	NSC**	NA
Muller-Fa□bender (30)	NA			NA	NA	NA	NA	NSC	NA
Mund-Hoym (31)	NA			NA	NA	NA	NA	NA	NA
Murad (12)	NA			NA	NA	NA	NA	NA	NA
Nguyen (13)	NA			NA	NA	NA	NA	NA	1.43
Noack (32)	NSC			NSC	NSC	NSC	NA	NSC	0.62
Pavelka (33)	NSC			NSC	NSC	NSC	NA	NA	0.56
Pouwels (18)	NSC			NA	NA	NA	NA	NSC**	NA
Pujalte (34)	NA			NSC	NSC	NSC	NA	NA	0.00
Qiu (35)	NA			NSC	NSC	NSC	NA	NA	NA
Reicheit (36)	NA			NA	NA	NA	NA	NA	NA
Reginster (16)	slightly lower			NSC	NSC	NSC	NA	NSC	0.82
Rindone (37)	NA			NA	NA	NA	NA	NA	0.50
Rovati (38)	NA			NA	NA	NA	NA	NA	0.62
Rovati 1 (39)	NA			NSC	NSC	NSC	NA	NA	0.62
Second study (39)	NA			NSC	NSC	NSC	NA	NA	0.71
Third study (39)	NA			NSC	NSC	NSC	NA	NA	NA
Scroggie (17)	HbA1c	NSC		NA	NA	NA	NA	NA	NA
Shankland (14)	NA			NA	NA	NA	NA	NA	NA
Tapadinhas (40)	NA			NA	NA	NA	NA	NA	NA
Thie (15)	NA			NA	NA	NA	NA	NA	NA
Yu (19)	97.2	97.2		NA	NA	NA	NA	NA	NA
Vajranetra (41)	NA			NA	NA	NA	NA	NA	NA
Vas (42)	NA			NA	NSC	NA	NSC	NSC	NA
Average	95.6	92.6							
No. with reports	4	4	9	11	13	10	3	6	18
Total patients			336	703	753	663	90	372	988
Total patient years			567	591	603	587	16	290	706

Abbreviations: NA, not available; NSC, not clinically significant; HbA1c, glycosylated hemoglobin; chem., chemistry; UA, urinalysis; occult blood, stool measurement; BP, blood pressure; P, pulse; GlucN/P, ratio of side effects from glucosamine divided by those from placebo.

Table 3. Overview of efficacy of glucosamine for arthritic complaints.

Study	Joints Evaluated	Arthritis Symptoms Significant difference
Braham(23)	knees	0.038
D'Ambrosio(1)	generalized OA	0.01
Das(24)	knees	0.04
Drovant(25)	generalized OA	0.005
Forster(26)	knees	sign diff (0.05)
Giordano(27)	generalized OA	0.001
Houpt(3)	Knees	NCS (0.1)
Hughes(28)	knees	NCS (0.1)
Leffler(29)	knees or back	0.02
Muller-Fa□bender(30)	knees	sign diff (0.05)
Mund-Hoym(31)	back	sign diff (0.05)
Noack.(32)	knees	0.05
Pavelka(33)	knees	0.01
Pujalte(34)	generalized OA	0.01
Qiu(35)	knees	sign diff (0.05)
Reicheit(36)	Knees	Sign diff (0.05)
Reginster(16)	Knees	sign diff (0.05)
Rindone(37)	knees	NCS (0.1)
Rovati (38)	knees	sign diff (0.05)
Rovati: First study(39)	knees	0.014
Second study(39)	knees	0.012
Tapadinhas(40)	generalized OA	0.001
Vajranetra(41)	knees	sign diff (0.05)
Average		0.040
Median		0.050
No. with reports		23
Total patients		2645
Total patient years		933

Abbreviations: NA= not applicable; OA, osteoarthritis; NA, not available; NCS, not clinically signficant

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