

**GLUCOSAMINE
& CHONDROITIN
SUPPLEMENTS
FOR JOINT HEALTH:
MISSED MESSAGES**

Luke Bucci, Ph.D, CCN, CNS.

Vice President, Research

Schiff Nutrition International

Salt Lake City UT

lukeb@schiffnutrition.com



4th Annual
ISSN
Conference
and Expo
June 10-12, 2007
Las Vegas, NV

Sponsor:
Schiff Nutrition International

Glucosamine & Chondroitin (GC) for Joint Health: Basic Facts – United States Market

- Classified as dietary supplement in United States (not a drug)
- In 2004, over 40 million 100 count bottles were sold
- Approx. \$1 billion yearly sales
- GC combination, often with other ingredients, is the norm
- Available in most major retailers, direct, online, MLM



Glucosamine & Chondroitin (GC) for Joint Health: Abbreviations

- EULAR = European League Against Rheumatism
- GAIT = Glucosamine/chondroitin Arthritis Intervention Trial
- GC = Glucosamine combined with Chondroitin sulfate, usually in daily doses of 1500 mg and 1200 mg, respectively, in 2-6 pills.
- GUIDE = Glucosamine Unum In Die Efficacy trial
- HA = Hyaluronan
- MSM = methylsulfonylmethane
- SAME = S-Adenosyl-L-Methionine
- VAS = Visual Analogue Scale
- WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Glucosamine & Chondroitin (GC) for Joint Health: Basic Facts – Europe

- G or CS used individually as first-line therapeutic agents for knee OA
- EULAR gave 1A Level of Evidence and A Strength of Recommendation
- Prescription drugs
- Different countries favor one or other
- GC combos not in use



Glucosamine & Chondroitin (GC) for Joint Health: Disparity between Medical Use in US, Europe

United States:

- Non-Rx supplement
- Not endorsed by any medical groups
- Retailers sell
- Less research
- Unknown \$ impact
- Not reimbursed
- Glucosamine HCL

Europe:

- Prescription only
- Endorsed by arthritis medical groups
- Drug companies sell
- Extensive research
- Reduces cost of OA
- Covered
- Glucosamine SO4

GC for Joint Health: Missed Headlines

- Glucosamine + Chondroitin better than Celebrex® !
- Glucosamine relieves pain better than the leading arthritis pain-relief drug !
- Glucosamine safe for diabetics !
- Glucosamine safe for persons with shellfish allergies !
- Glucosamine prevents joint replacements !

GC for Joint Health: Missed Message #1

GC Efficacious for mod-severe OA

- From NIH GAIT Human Clinical Study
- Started in 1998, 1st presented November 2005 (ACR mtg)
- Clegg DO, et al. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. *NEJM* 2006 Feb23; 354(8):795-808.
- Compared placebo, Glucosamine HCL, Chondroitin sulfate, GC, celecoxib (Celebrex) for 6 months
- n=1583 total subjects knee OA (n=1229 mild pain, n=354 moderate-severe pain), 59 year average age
- 1° endpoint - % subjects >20% decrease in VAS pain

GC for Joint Health: Missed Message #1

GC Efficacious for mod-severe OA

- NIH GAIT Human Clinical Study results
- 1^o endpoint = % subjects >20% decrease in WOMAC pain:
 - All subjects – Celebrex only group with significant difference from placebo (10% higher) (70.1 vs. 60.1%, P=0.008 by 2-sided Chi-square, alpha=0.017)
 - GC 66.6 vs. 60.1% responders, P=0.09
- GAIT investigators expected and powered for 35% placebo response rate – got 60%
- Placebo ≠ inert – all groups took 1.2 500mg acetaminophen tabs daily (baseline) and 1.6-1.9 tablets after 6 months
- What would 1000 mg acetaminophen do for your minor joint pain?

GC for Joint Health: Missed Message #1

GC Efficacious for mod-severe OA

- NIH GAIT Human Clinical Study results
- Overall – OMERACT/OARSI response rate
 - GC trended better than placebo (65.6 vs. 56.9%, $P=0.02$)
- Subgroup analysis – moderate-severe pain
 - GC only group significantly different from placebo (79.2 vs. 54.3% responders, $P=0.002$)
 - GC only group with more subjects >50% improvement in WOMAC Pain scores (52.8 vs. 32.9%, $P=0.02$)
 - GC only group for likelihood of response (98.3% CI) for 1° and OMERACT/OARSI measurements

GC for Joint Health: Missed Message #1

GC Efficacious for mod-severe OA

- What the public heard:
- “Glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee.” – NIH GAIT NEJM abstract, February 23, 2006
- “Supplements fail to help mild knee arthritis: study” – Reuters, February 22, 2006
- “Study: Supplements little help for arthritis” – Associated Press, February 22, 2006
- “Supplements Fail to Stop Arthritis Pain” – New York Times, February 23, 2006
- “Joint Dispute: Early Results of Arthritis Trial Show Little Benefit for Glucosamine, But the Industry Is Already Spinning” – Washington Post, November 22, 2005

GC for Joint Health: Missed Message #1

GC Efficacious for mod-severe OA

- What the public missed:
- “Exploratory analyses suggest that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain.” – NIH GAIT NEJM abstract, February 23, 2006
- “Fine Print Sends Clear Message: Stay the Course” – Jane Brody, New York Times, March 14, 2006
- “...it did find that the combination of the two supplements provided significant relief for people with moderate-to-severe pain.” – Arthritis Foundation statement, February 22, 2006
- “Supplements may help relieve moderate-to-severe knee pain” – Wall Street Journal, February 23, 2006
- “Efficacy of Glucosamine and Chondroitin Sulfate may depend on level of osteoarthritic pain.” – NIH News, February 22, 2006 & NCCAM website

GC for Joint Health: Missed Message #1

GC Efficacious for mod-severe OA

- What the public missed:
- Need for ANYTHING that works safely to reduce OA pain
- Other findings of Glucosamine or Chondroitin slowing or stopping cartilage loss in OA were seldom reported
- Nobody seemed to explain the failure of medical treatments to slow or stop progression of OA to immobility and joint replacements
- No drugs (especially the ones usually prescribed or used) have been shown to halt cartilage loss – also not reported (e.g., minocycline)
- Benefits for moderate-to-severe pain subjects is critical – this is the group that medicates for long time periods, leading to drug toxicity
- Safety of G, CS, GC was reconfirmed and reported by GAIT study

GC for Joint Health: Missed Message #2 Glucosamine as good as Celebrex®?

	Placebo	GC	Celebrex
% >20% ↓ WOMAC Pain	60.1	66.6	70.1
P value	- - -	0.0906	0.008
% ↓ WOMAC Pain Score	36.3	42.2	42.4
P value	- - -	0.12	0.12

- All subjects (235/500 by WOMAC Pain)
- Same Chi-square analysis between GC, Celebrex groups gave P=0.31, not significantly different for primary endpoint

GC for Joint Health: Missed Message #2 Glucosamine as good as Celebrex®?

	Placebo	GC	Celebrex
% >20% ↓ WOMAC Pain	54.3	79.2	69.4
P value	- - -	0.002	0.06
% ↓ WOMAC Pain Score	36.0	51.9	44.8
P value	- - -	0.009	0.18

- Moderate-to-severe pain group (340/500 by WOMAC Pain)
- Same Chi-square analysis between GC, Celebrex groups give P=0.18, not significantly different for primary endpoint

GC for Joint Health: Missed Message #3

Glucosamine bested Acetaminophen

- From GUIDE Human Clinical Study
- Started in May 2000, 1st presented November 2005 (ACR meeting), published a year later than NIH GAIT study
- Herrero-Beaumont G, et al. Glucosamine Sulfate in the Treatment of Knee Osteoarthritis Symptoms. A Randomized, Double-Blind, Placebo-Controlled Study Using Acetaminophen as a Side Comparator. *Arth Rheum* 2007 Feb; 56(2):555-567.
- Compared placebo, Glucosamine SO₄ (1500 mg/d), Acetaminophen (3000 mg/d) for 6 months
- n=318 total subjects knee OA, 64 year average age
- 1^o endpoint – Lequesne Algofunctional Index
- ***Ibuprofen rescue medication

Glucosamine & Chondroitin (GC) for Joint Health: Disparity in Rescue Medication Use in US, Europe

United States (GAIT):

- Acetaminophen
- up to 4000 mg daily
- *24 hour washout before evaluation*
- Use increased in all groups from 1.1-1.2 to 1.6-1.9 500 mg tabs/d
- Average usage ~20% of max

Europe (GUIDE):

- Ibuprofen
- 400 mg every 8 hours
- Max 3 days intake
- 7 day washout before resume
- *7 day washout before evaluation*
- 0.2-0.26 tablets daily
- Average usage ~20% max

GC for Joint Health: Missed Message #3

Glucosamine bested Acetaminophen

	Placebo	GS	Paracetamol
ITT/PP LAI	-1.9/-2.8	-3.1/-4.3	-2.7/-3.6
ITT P vs. Placebo	- - -	0.032	0.18
PP P vs. Placebo	- - -	0.01	0.26

- WOMAC, MCII, PASS results consistent with Lequesne Algofunctional Index (LAI) results
- “The efficacy results obtained with glucosamine sulfate were significant and clinically relevant in the present study in which acetaminophen, the currently recommended preferred medication (2,3), was used as a side comparator.”

GC for Joint Health: Missed Message #3

Glucosamine bested Acetaminophen

	Placebo	GS	Paracetamol
↑ Liver Enzymes	6	2	21
No rescue meds	9%	22%	21%
OARSI-A	21.2%	39.6%	33.3%
GAIT OARSI-A	42.2%	46.4%	50.0% (Celebrex)

- Glucosamine safer on liver function
- GS OARSI-A responders P=0.004 vs. placebo
- Acetaminophen OARSI-A responders P=0.047

GC for Joint Health: Missed Message #3

Glucosamine bested Acetaminophen

- What the public missed:
- Everything
 - Virtually no media coverage
 - No discussion in medical groups
 - Difference in rescue med practices may account for inability of US studies to find pain efficacy for GC in light of huge, so-called “placebo” responses

GC for Joint Health: Missed Message #4

Glucosamine = Fewer Joint Replacements

	Placebo	GS	95% CI
Total knee replacement	11 (16.4%)	3 (4.3%)	0.27 (0.08-0.91) P=0.021
Total knee or hip replacement	13 (19.4%)	5 (7.2%)	0.37 (0.14-0.99) P=0.036
n	67	69	79%

- 5-year follow-up of Pavelka 3 year GS study
- 73% reduction in risk of total knee replacement
- Which group would you want to be in?
- Pavelka K, et al. Glucosamine sulfate prevents total joint replacement in the long-term follow-up of knee osteoarthritis patients. *American College of Rheumatology Annual Meeting* 2004 Oct16-21; San Antonio, TX, Abstract 251, poster 252.

GC for Joint Health: Missed Message #4

Glucosamine = Fewer Joint Replacements

	Placebo	GS	RR
Total knee or hip replacement	12 (20.0%)	7 (13.4%)	0.55 P=0.18
Any surgery hip or knee	17 (28.3%)	9 (13.4%)	0.52 P=0.06
Evaluable/starting patients n	60/106	67/106	

- 5-year follow-up of Reginster 3 year GS study
- ~50% reduction in risk of joint surgery
- Which group would you want to be in?
- Reginster J-Y, et al. Current concepts in the therapeutic management of osteoarthritis with glucosamine. *Bull Hosp Jt Dis* 2005; 63(1-2); 31-36.
- Altman RD, et al. Total joint replacement of hip or knee as an outcome measure for structure modifying trials in osteoarthritis. *Osteoarth Cartilage* 2005 Jan; 13(1):13-19.

GC for Joint Health: Missed Message #5

Lack of Allergic Reactions from GC

- What reviewers wrote:
- “Do not use if you have shellfish allergies (Jellin et al. 2003).” – Health Canada 2004
- “Patients who are allergic to shellfish should not use glucosamine because it is derived from crustacean chitin.” – Hooper 2001 494
- “In addition, individuals with shellfish allergy should be cautious about use of glucosamine products, many of which are derived from shellfish.” IOM/NRC 2004

GC for Joint Health: Missed Message #5

Lack of Allergic Reactions from GC

- What the public missed:
- “This study demonstrates that glucosamine supplements from specific manufacturers do not contain clinically relevant levels of shrimp allergen and therefore appear to pose no threat to shrimp-allergic individuals” – Villacis 2006 1457
- “All 6 had negative skin test responses to the glucosamine extract (Table 1) and uneventful oral challenges with glucosamine, with no changes in skin, vital signs, or spirometry.” – Gray 2004 459

GC for Joint Health: Missed Message #6

Lack of Glucose/Insulin Effects for GC

- What reviewers wrote:
- “One potential problem with a glucose-derived nutraceutical, such as glucosamine, is the potential disturbance of systemic glucose metabolism.” – Goggs 2005 145
- “Glucosamine ... may increase insulin resistance, as suggested in animal experimental studies using suprapharmacological intravenous doses of the compound [84].” – Herrero-Beaumont 2007 215
- “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). – Cochrane Review Towheed 2005
- “Consult a health care provider prior use if you have diabetes (Jellin et al. 2003).” – Health Canada 2004
- “However, it [glucosamine] can worsen insulin resistance, so it should therefore be used cautiously by patients who have diabetes.” – Hooper 2001 494

GC for Joint Health: Missed Message #6

Lack of Glucose/Insulin Effects for GC

- What the public missed:
- “This study demonstrates that oral glucosamine supplementation does not result in clinically significant alterations in glucose metabolism in patients with type 2 diabetes mellitus.” – Scroggie 2003 1587
- “Despite theoretical risks based on animal models given high intravenous doses, glucosamine/chondroitin (1500 mg/1200 mg daily) does not adversely affect short-term glycemic control for patients whose diabetes is well-controlled, or for those without diabetes or glucose intolerance (SOR: A, consistent, good-quality patient-oriented evidence).” – Marshall 2006 1091
- “Our study adds to previous reports^{12 13} that oral doses of glucosamine taken over a period of time have little or no significant effect on glucose metabolism in people who are neither diabetic nor glucose intolerant.” – Biggee 2007 260
- Over 14 million prescriptions of GS have been given in Europe from 1995-2005 and closely monitored by drug surveillance programs without evidence of adverse effects, including diabetics.

GC for Joint Health: Missed Message #7

Matching in vitro doses with mechanisms

- “It [serum glucosamine concentration post supplementation] is far below most of the concentrations used in in vitro cell or tissue culture incubations by others, usually for days or weeks, in proposing mechanisms to protect chondrocytes, inhibit chondroitin degradation, diminish inflammation, or provide immunosuppression in articular cartilage.” – Biggee 2006 222
- “As in healthy volunteers, endogenous glucosamine is present in plasma of knee osteoarthritis patients and reaches concentrations in the 10 μ M range after repeated oral doses of crystalline glucosamine sulfate. Glucosamine concentrations in the 10 μ M range are effective in selected human chondrocyte models.” - Persiani 2005 P184

GC for Joint Health: Missed Message #8

Sports Nutrition Settings

- 52 of 68 teen athletes with chondropathia patellae had complete remission of symptoms and resumed training after 5 months (Bohmer 1982 4897 Therapiewoche) – open trial
- Case study: 56 y male active tennis player took GC for 2 y. MRI before, after showed decreased size protrusion, brighter signal (repair) of L3-4 disc. No change in fully degenerated L4-5 disc. – van Blitterswijk 2003 BMCComplAltMed

GC for Joint Health: Missed Message #9

Negative Bias and Halo Effects

- Finding: positive studies on GC have been associated with industry sponsorship, null studies with academic sponsorship
- Premise: Bias works both ways – do investigators in null studies have potential bias or halo effects?

GC for Joint Health: Missed Message #9

Negative Bias and Halo Effects

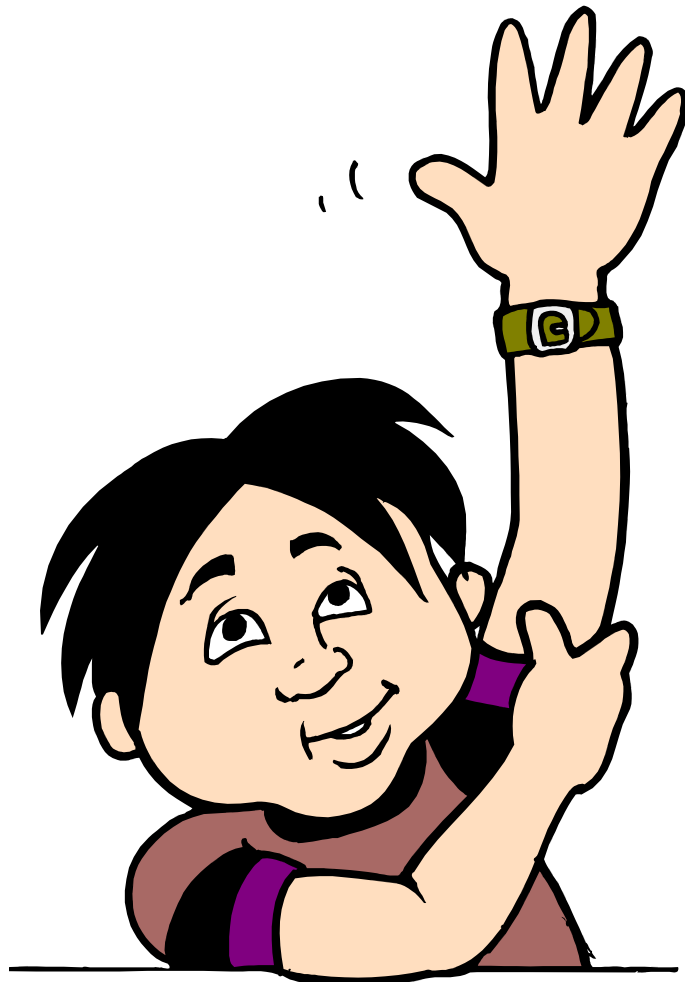
- NIH GAIT study: most investigators disclosed ties to pharmaceutical companies and prescribed drugs that compete with GC for consumer use in joint care
- Several NIH GAIT investigators authored unfavorable reviews on GC while conducting the study at their site
- Reviewers with critical opinions of GC literature are dependent on government and pharmaceutical company funding for their research into finding new ways to treat OA, and have a vested interest in downplaying current treatment modalities that will lessen their ability to patent and commercialize new agents
- Remember that pharmaceutical companies from Europe sponsored positive studies on GC, similar to NSAIDs and COX2 inhibitors.

Glucosamine & Chondroitin (GC) for Joint Health: Is the Glass Half Full or Half Empty?

- GC supplements have survived 15 years in spite of no medical support, out-of-pocket expense, negative media, and cheaper Glucosamine supplements
- Veterinary industry use of GC ignored – animals do not lie



Any Questions or Comments?



issn

international society of sports nutrition™

Email:

lukeb@schiffnutrition.com