

(Handout is 22 pages total)

EVIDENCE FOR THE USE OF GLUCOSAMINE AND CHONDROITIN SULFATES IN PATIENTS WITH OSTEOARTHRITIS

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Course content:

This course provides a thorough investigation of the research evidence for the use of glucosamine and chondroitin sulfates for the treatment of Osteoarthritis (OA). The research discussed will enable the participants to understand and communicate accurate information to patients regarding the evidence-based indications and contraindications for these dietary supplements. Cases will be used to discuss patients who are taking these supplements (and likely other medications as well) and the impact on physical therapy care. Additionally, valid and reliable sources of information will be presented to foster participant's own investigations of alternative therapies.

Learning Objectives:

Upon completion of this course, the participant will be able to:

1. Describe FDA regulation of dietary supplements.
2. Discuss the evidence-based indications (what types of patients; what types of OA; expected results; frequency and duration of dosage; cost) for the use of glucosamine and chondroitin sulfate in patients with osteoarthritis.
3. Analyze the reliability and validity of internet resources for drug/supplement information
4. Educate patients as to the evidence based indications for the use of glucosamine and chondroitin sulfate as well as how to find reliable and valid information on their own.

Glucosamine and Chondroitin Sulfates in the Treatment of Osteoarthritis: An Evidence Based Review

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Our patients are taking Glucosamine and Chondroitin Sulfate^{36,43,54,98}

Why Glucosamine and Chondroitin Sulfate for Patients with Osteoarthritis?

Osteoarthritis (for review: 33,79)

- Degenerative Joint Disease
- American College of Rheumatology (ACR)
 - Heterogeneous group of conditions that lead to joint signs/symptoms associated with defective articular cartilage integrity and changes in underlying bone
- 30% of people over 65 have radiographic signs of OA but only 1/3 have symptoms
 - Poor correlation between disease severity on X-ray and severity of symptoms

Osteoarthritis (for review: 33,79)

- Clinical manifestations
 - Pain
 - Aching; poorly localized
 - Typically increases with activity and decreases with rest
 - May awake at night
 - Stiffness
 - Reduced ROM, muscle weakness
 - Inflammation (acute or subacute)
 - Crepitus

Articular Cartilage (for review: 29)

Osteoarthritis and Articular Cartilage (for review: 33,79)

- Imbalance of degradation and proper repair
 - Loss of GAGs, PGs
 - Dehydration/Loss of swelling pressure
 - Chondrocyte insufficiency +/- or death
 - Increased levels of degradative enzymes
 - Collagenase, aggrecanase, matrix metalloproteinases
 - Aseptic inflammation of the synovium
 - Subchondral bone collapse
 - Bony cysts and osteophytes

Why Glucosamine and Chondroitin Sulfate for Patients with Osteoarthritis?

Glucosamine (GlcN) (for review 14,15)

Endogenous element of connective tissue extracellular matrix (ECM)

- Small, amino-monosaccharide constituent of glycosaminoglycans (GAGs)
 - ...Replace building blocks that are depleted in OA
- For supplementation it is synthesized from crustacean shells (chitin)
 - Hydrolyzed from shells with sulfuric acid (GlcN sulfate) or hydrochloric acid (GlcN hydrochloride)

Glucosamine

- Animal & *in vitro* evidence suggests GlcN
 - Increases GAG (CS) levels^{9, 84}
 - Doesn't increase CS levels^{60, 61}
 - Increases aggrecan levels³⁴
 - Reduces enzymes responsible for ECM degradation^{34,37,78}
 - Suppression of certain immune cell types^{40,53}

Glucosamine

■ Studies in humans

- Study in 18 healthy subjects after 1.5g oral GlcN demonstrated serum concentrations of 1.9-11.5 μ M¹³
 - Lower serum concentrations than those in previous *in vitro* studies
 - Does glucosamine have the same effects *in vivo*?
- Exogenous GlcN accounts for less than 2% of GAGs with 12 μ M incubation^{60, 61}

Chondroitin Sulfate (CS)

(for review 42,47)

■ Endogenous element of connective tissue ECM

- Large, - charged, glycosaminoglycan (GAG) that can exist in various (4, 6 sulfate most common)
 - ...Replace building blocks that are depleted in OA
- For supplementation it is synthesized from bovine trachea (rarely pork by-products and shark cartilage) and is altered to reduce molecular weight

Chondroitin Sulfate

■ Animal and *in vitro* evidence suggests

- Stimulates formation of PGs and aggrecan^{9, 96}
- Inhibit degradative enzymes^{8-10, 23}
- Reduces macrophage and neutrophil infiltration⁷⁴
- Stimulates HA⁹⁶

■ Studies in humans

- Oral CS showed no effect on GAG serum levels^{6,27-28}

Does Orally Administered Glucosamine and Chondroitin Sulfate Reach the Articular Cartilage?

Glucosamine

■ Oral bioavailability and presence in the articular cartilage of the knee

- Oral GlcN is absorbed in the GI tract and incorporated in plasma proteins, but no studies have demonstrated free GlcN in the plasma^{82-83,85}
- Absolute oral bioavailability for GlcN-S from 26-44%^{27,30,64,96} and GlcN-H from 12-21%^{6, 73}
- Radiolabeling of exogenous GlcN demonstrates presence in articular cartilage but also in other tissues⁸¹

■ Available in the US as capsules, tablets, liquid and powders

Chondroitin Sulfate

■ Oral bioavailability and presence in the articular cartilage of the knee

- Depends on molecular weight of product⁶
- Evidence in animals^{28,65} & humans^{27,97} ~12-14% CS absorbed after oral administration^{2, 74}
- Oral CS \uparrow plasma, synovial and cartilage concentrations of CS^{27,31,74}

- Available in capsules, tablets and powders

How Will We Know Glucosamine and Chondroitin Sulfate Are Working?

Measuring Change in Patients with OA

- Pain Visual Analog Scale (VAS)
- Lequesne Algofunctional Index (LI) 48-50
- Subjective responses by patients with respect to pain, maximum distance walked, and ADLs
 - ≥14 = extremely severe
 - 8-10 = severe
 - 1-4 = mild

Measuring Change in Patients with OA

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) ¹¹
 - Subjective responses by patients using Likert scale or VAS form with respect to pain, stiffness, physical function, social function and emotional function
- Less NSAID/Analgesic use
- Radiographic changes in joint space
 - In most studies, X-ray is taken in a position of extension
 - Patients in pain may not be able to fully extend
 - Is hyaline cartilage thickness \propto joint space on X-ray? ^{1,14,21}
 - Is this measure clinically relevant? ^{12,18,21,24}

Measuring Change in Patients with OA

- Effect Size (*from Cohen et al 1977*)
 - The strength or magnitude of the difference between two sets of data
 - Facilitates comparisons of efficacy between studies

Glucosamine:

Evidence from Clinical Trials

Glucosamine

Meta-analyses

McAlindon et al 2000 ⁵²

- 6 RCTs: GlcN oral or IA for knee OA (5/6 had manufacturer affiliation)
 - GlcN v PBO (pain) $d=.51$
 - GlcN v PBO (LI) $d=.41$
- Lower the quality the study, the higher its results ($p=.01$)
- Authors conclude that assessment of methodology suggests actual efficacy is much smaller

Glucosamine

Meta-analyses

Hauselmann 2001 ³⁸

- All RCTs
 - GlcN (pain) pooled effect size $=.56$
- When author used only recent, high quality studies
 - GlcN (pain) pooled effect size $=.26$

Glucosamine Meta-analyses

- *Towheed et al 2005*⁹⁰
 - High quality RCTs (GlcN vs. PBO)
 - Significant difference (SD)
 - n=8, LI: smd = -.61
 - n=2, JSN: smd = .24
 - No significant difference (NSD)
 - n=8, Pain: smd = -.19
 - n=5, WOMAC: smd= -.15

Glucosamine Meta-analyses

- *Towheed et al 2005*⁹⁰
 - Varying quality RCTs (GlcN vs. NSAID)
 - GlcN significantly superior to reduce pain
 - n= 3, smd = -.40
 - GlcN not significantly superior to improve LI
 - n=2, smd = -.36
 - All studies reported significant differences in number of reported adverse events

Glucosamine- Summary

- GlcN for ↓ pain
 - No effect .19 to moderate effect .51
- GlcN for ↓ pain & ↑fxn (LI)
 - Moderate effect .41 to .61
- GlcN for ↓ pain, ↓stiffness & ↑fxn (WOMAC)
 - No effect .15
- GlcN vs. NSAIDs to ↓ pain & ↑fxn (LI)
 - Moderately superior or = for pain relief .40
 - Moderate superior for LI .36

Glucosamine- Summary

- Comment and controversy^{7,14,15,18,22,31-2,42,45-6,64}
- Advantages: younger individuals, of normal weight and with less severe OA (grades II-III)
 - **1.5g/day (500mg 3Xday)**
 - Slow acting—take for at least 4 weeks
 - Effects continue after cessation for at least 4 weeks
- Bellamy and Lybrand 2001
 - Potential for benefit with little risk of adverse effects for some patients
 - Adjunct to proven therapies (PT)

Glucosamine- Potential Adverse Effects

- *Towheed et al 2005*⁹⁰ n=1145
 - 26% GlcN reported adverse event vs. 32% PBO

- Most common patient complaints are GI related
 - Diarrhea, constipation, nausea, abdominal pain
 - In contrast to the varied and potentially serious adverse effects of NSAID therapy
- Patients allergic to shellfish should not take GlcN

Glucosamine-

Potential Adverse Effects

- Immunosuppressive effects?
 - Suppression of certain immune cell types (T lymphoblasts, macrophages, dendritic cells)^{40,53}

Glucosamine-

Potential Adverse Effects

- Alteration of glucose metabolism and insulin activity?
 - Glucosamine has a similar role to glucose in metabolic pathway thought to regulate cellular utilization of glucose
 - Some authors report GlcN alters glucose transport and insulin secretion (which would lead to hyperglycemia)^{57,73,75,86} and some show no alteration^{35,58,67,73}

Glucosamine-

Potential Adverse Effects

- NSD in serum insulin or glucose after 1.5g/day oral GlcN, X 12 wks in 11 healthy individuals vs PBO⁸⁷
- NSD glycosylated hemoglobin levels after 1.5g/day oral GlcN X 12 wks (*note: dose also included 1.2g CS*) in 22 diabetic individuals⁸⁰
- No evidence of LT glucose effects after 3 years of supplementation in healthy individuals (1.5 g/day)^{20,70,66}

Chondroitin Sulfate:

Evidence from Clinical Trials

Chondroitin Sulfate

Meta-analyses

Leeb et al 2000⁴⁷

- 6 RCTs: CS 800-1200mg/day, 90 days to 1 year, for OA hip and knee
 - CS (pain) d=.9
 - CS (LI) d=.74
 - 5/6 groups SD in patient global assessment
 - 4/6 groups SD in physician global assessment
- No formal article validity assessment
- Author concludes good evidence that CS is effective in treatment of OA

Chondroitin Sulfate

Meta-analyses

McAlindon et al 2000⁵²

- 8 RCTs: CS oral or IM for knee OA (5/6 had manufacturer affiliation)
 - CS v PBO (pain) d=.86
 - CS v PBO (LI) d=.41
 - Lower the quality the study, the higher its results (p=.01)

- Authors conclude that assessment of methodology suggests actual efficacy is much smaller

Chondroitin Sulfate

Meta-analyses

***Hauselmann 2001*³⁸**

- All RCTs
 - CS (pain) pooled effect size $d = 1.37$
- When author used only recent, high quality studies
 - CS (pain) pooled effect size $d = .37$

Chondroitin Sulfate

Clinical Trials

■ *Michel et al 2005*⁵⁶

- $n=300$, .8g/day X 2 years, knee OA
 - SD in joint space narrowing (mean/min) for PBO over 2 year period, but NSD in CS group ($p=.04$, .05)
 - JS as measured on X-ray by computer: patient in standing, partial knee flexion
 - CS (JSN): $0.0 \pm .53\text{mm}$
 - PBO (JSN): $.14 \pm .61\text{mm}$ ($p=.001$)

Chondroitin Sulfate

Clinical Trials

■ *Uebelhart et al 2004*⁹¹

- $n=110$, .8g/day X2, 3mo. periods X 1 yr
 - CS (LI): $\downarrow 3.2$ vs $\downarrow 1.9$ PBO ($p<.01$)
 - SD only at 9 and 12mo. tests
 - CS (pain): $\downarrow 24.5$ vs $\downarrow 15.3\text{mm}$ PBO ($p<.05$)
 - SD only at 9 and 12mo. Tests
 - CS (JSN): $-.19$ vs PBO -4.55mm PBO ($p=.06$)
 - Measured in standing, knee extended
 - SD in paracetamol use CS vs PBO after 1 mo.

Chondroitin Sulfate

Clinical Trials

■ *Morreale et al 1996*⁵⁹

- $n=146$, knee OA
 - LI, Pain, Pain on loading & Paracetamol use
- DS reduced pain rapidly but pain returned after cessation
- CS reduced pain more slowly but continued to do so up to 3 months after cessation

Chondroitin Sulfate- Summary

- CS for \downarrow pain
 - From small .37 to large effect .86/.90
- C for \downarrow pain & \uparrow fxn (LI)

- From moderate .41 to large effect .74
- CS for JSN ^{56,91}
 - Significant difference from PBO
- CS vs. NSAIDs/Analgesics
 - ↓ paracetamol use ⁹¹
 - Equal and more prolonged effects ⁵⁹

Chondroitin Sulfate- Summary

- Comment and controversy ^{18,22,31-2,42,45-6,64}
 - Need more long term research (longest study is 2 years)
- Advantages: younger individuals, of normal weight and with less severe OA (grades 2-3)
 - **800mg-1.2g/day (400mg 2-3Xday)**
 - Slow acting—take for at least 4 weeks
 - Effects continue after cessation for at least 4 weeks

Chondroitin Sulfate- Potential Adverse Effects

- Current evidence demonstrates short term and long term (1-2 year) safety ^{47,56,91}
 - In contrast to the varied and potentially serious adverse effects of NSAID therapy
 - No evidence of adverse effects over PBO in any study reviewed
 - Most common complaints are GI related
 - Diarrhea, constipation, nausea, abdominal pain
- Product infection with BSE is unlikely ⁸⁸

What if I take BOTH Glucosamine & Chondroitin Sulfate?

Combination Trials (GlcN + CS)

Meta-Analysis

- *Richy et al 2003* ⁷¹
 - 8 RCTs, CS .8-2.0g/day, GlcN .75-1.5g/day ≥4 weeks, knee OA
 - Pooled GlcN and CS articles
 - LI d=.43
 - WOMAC d=.30
 - VAS Pain d=.45
 - VAS Mobility d=.59

Combination Trials (GlcN + CS)

- *Blitterwijk et al 2003* ¹²
 - Case report of 56y/o man with 15 hx of LBP
 - GlcN 1.5g, CS 1.2g/day X 9mos then GlcN .75g, CS .8g/day X 15 mos
 - Pt began to ‘feel better’ after 6mos.
 - Per report pt could ‘withstand heavier work loads without pain’
 - MR findings: ‘improvement in structural quality of disc cartilage’; ‘protrusions decreased over time’

Combination Trials (GlcN + CS)

- *Das & Hammad 2000*³⁰
 - N=93, GlcN 1.5g/day and CS 1.2g/day X6mos, knee OA (K&L grades 2-4)
 - Mild-Mod OA (LI): Rx ↓2.8 vs ↓1.4 PBO (p=.04)
 - Severe OA (LI): NSD
 - Mild-Mod & Severe OA (WOMAC): NSD
 - Mild to Mod patients: >25% improvement in global assessment of their OA (VAS) was SD than PBO (70% vs 46% respectively; p=.04)

Combination Drugs (GlcN +CS)

Potential Adverse Effects

■ Alteration of Blood Coagulation

- Case report of patient on warfarin^{76,81}
 - Significant alteration of INR (2.53 to 4.53) after 3.0g glucosamine AND 2.4g chondroitin sulfate for 4 weeks
 - 2X current ‘therapeutic’ dose of GlcN and CS

Why is the Research for Glucosamine and Chondroitin Sulfate Controversial?

Research Issues

- Use of European research in US market
 - Supplements are not regulated by FDA, and quality control is a huge issue
 - Studies use primarily European manufacture supplements which are Rx in those countries
- Manufacturer affiliations
- Control of other medications and therapies
- Use of subjective +/-or invalid measurement tools
- Statistical Significance vs Patient Significance vs Clinical Significance

Governing Medical Association’s Recommendations

- American College of Rheumatology Subcommittee on OA Guidelines (2000)⁵
 - “While a number of studies support the efficacy of both GlcN and CS for palliation of joint pain in patients with knee OA, the subcommittee believes that it is premature to make specific recommendations about their use at this time because of methodological considerations...”

Governing Medical Association’s Recommendations

- European League Against Rheumatism (EULAR) Recommendations (2003)⁴⁴
 - Acetaminophen is the oral analgesic to begin first and if successful is the preferred long term treatment
 - NSAIDs should be considered in patients unresponsive to (1)
 - Opioid analgesics are useful alternatives to (1) and (2)
 - GlcN and CS have symptomatic effects and may modify structure OA

An answer soon?

■ NIH-NCAAM GAIT Trial

- Multicenter (n=13), randomized, double-blind study
 - GlcN alone
 - CS alone

- GlcN and CS
- Celecoxib alone
- PBO

How Do I Handle My Patient's Questions Now?

Patient Cases

Case One

- 60 year old man with diagnosis of R knee OA. Currently on NSAIDs for treatment but has been experiencing increasing GI symptoms. MD prescribed proton pump inhibitor (Prilosec®).

Patient Cases

Case Two

- 65 year old otherwise healthy woman with diagnosis of B OA hands. Patient has been a seamstress for 40 years and has noticed pain and stiffness that has progressed to limiting her sewing activity.

Patient Cases

Case Three

- 52 year old obese female with PMH of Type 2 Diabetes and B hip OA. Currently taking an oral hypoglycemic drug (Glucophage®) as well as OTC NSAIDs (Aleve®) as needed for hip pain. At the advise of her MD, she began a weight reduction program, with an RD and joined a gym 1 month ago (treadmill, elliptical and low impact aerobics). She comes to you having stopped all exercise 2 weeks ago secondary to R hip pain after exercise.

Patient Cases

Case Four

- 71 year old man with significant history of CABGX2, Atrial Fibrillation and CHF. Current medications include Lipitor®, Coumadin®, and Lotensin® and Vicodin®.
- MD referral to PT indicates diagnosis of severe B knee OA. Patient has had therapy in the past with success but HEP is not maintaining pain-free ADLs. MD also indicates that TKR is being considered but is not ideal secondary to patient's cardiac comorbidities.

Patient Cases

Case Five

- 42 year old ex-athlete (college and semi-pro football) with history of ACL reconstruction RLE. He currently wears brace with sporting activities—Softball in Spring/Summer and Basketball in Fall/Winter.

Advising Patients

- In the US, manufacturer quality is not assured
 - Analysis of the actual content of GlcN and CS supplements were significantly different from label claim in some products³
 - Some products had 0% active ingredient and others had as much as 115% active ingredient
 - Consumerlab.com study showed 4 products on US market did not contain the amounts of active ingredient claimed (from 0% to 85%)

Advising Patients

- Counsel patients to talk to their doctor
 - Emphasizing thorough past medical history and current Rx and OTC medications
 - Inform of any adverse effects
 - any supplement potent to have physiological effects can also be strong enough to harm
- Don't stop current therapies unless directed by MD
- Inform patients if you are knowledgeable
 - Characteristics that seem to garner a better result and dosing that is required ¹⁶
- Advocate for your patients' control of health care decisions
 - Help them obtain valid information on their own

How Can You Keep Up to Date on Issues Regarding Supplements?

Searching for Research Articles

- Formulate a specific clinical question
- Gather current published evidence that might answer that question
- Evaluate the gathered evidence to determine what is the “best” evidence to answer the question
- Interpret the evidence to determine a possible answer to the question

Searching for Research Articles

- At the Library and on the Internet:
 - Databases:
 - Medline (1966-)
 - CINAHL (1982-)
 - Sports Discus
 - AltHealthWatch—complementary/integrative medicine
 - Health Source
 - Consumer edition— health periodicals (1985-)
 - Academic edition—journals (3/4 peer reviewed; 1975-)
 - PEDro
 - The Cochrane Library

Searching the Internet

- Consumer Oriented Internet Sources
 - Stick to known quantities
 - Government run sites (.gov)
 - Associations, Foundations (.org)
 - Reliability and Validity—How do you know what your getting?
 - National Center for Complementary and Alternative Medicing (NCCAM)
 - Health on the Net Foundation (HON)
 - American Medical Association (AMA)

Searching the Internet

- NCCAM
 - Who runs the site?
 - Who pays for the site?
 - What is the purpose of the site?

- Where does the information come from?
- What is the basis of the information
- How is the information selected?
- How current is the information?
- How does the site choose links to other sites?

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Internet Resources for Medical and Health Information

Consumer Based and Governmental

Combined Health Information Database

<http://chid.nih.gov/index.html>

MedlinePlus

<http://www.medlineplus.org/>

The American Medical Association

<http://www.ama-assn.org/>

American Academy of Orthopedic Surgeons

<http://www.aaos.org/wordhtml/home2.htm>

The American Botanical Council

<http://www.herbalgram.org/>

National Center for Complementary and Alternative Medicine

<http://nccam.nih.gov/>

FDA: Office of Nutritional Products, Labeling and Dietary Supplements

<http://vm.cfsan.fda.gov/~dms/supplmnt.html>

Consumer Lab

<http://www.consumerlab.com>

Finding Clinical and Basic Science Literature

PubMed (search MEDLINE, CINAHL etc)

<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>

*tip: try using the clinical queries search filter (left frame)

*keep updated with PubCrawler: receive regular updates on clinical interests

<http://www.pubcrawler.ie>

The Cochrane Library

<http://www.cochranelibrary.com>

NIH Clinical Trials

<http://www.clinicaltrials.gov>

Agency for Healthcare Research and Quality (AHRQ)

<http://www.ahrq.gov/clinic/epcix.htm>

PEDro

<http://ptwww.cchs.usyd.edu.au/pedro>

<http://www.rehabtrials.org>

<http://www.nettingtheevidence.org.uk>

Database of Abstracts of Reviews and Effectiveness

<http://nhscrd.york.ac.uk/darehp.htm>

UT Sum Search

<http://sumsearch.uthscsa.edu/searchform45.htm>

Evidence Based Medicine Toolkit

<http://www.med.ualberta.ca/ebm/ebm.htm>

Websites with Tips for Evaluating Reliability and Validity of Medical and Health Information on the Internet

Health on the Net Foundation

<http://www.hon.ch/HONcode/>

National Council Against Health Fraud

<http://www.ncahf.org/>

<http://www.quackwatch.org/>

AMA Guidelines for medical sites on the internet

<http://www.ama-assn.org/ama/pub/category/1905.html>

http://www.wayne-health.org/nf/nf-wc_HealthSiteEvaluation.html