

Supplements in Osteoarthritis

Matthew Gammons, M.D.
Vermont Orthopaedic Clinic
Killington Medical Clinic
iSport



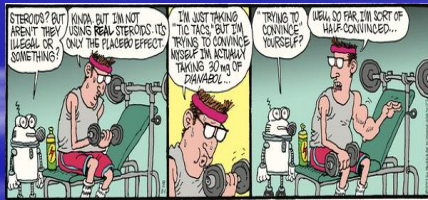
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Neither I, **Matthew Gammons**, nor any family member(s), have any relevant financial relationships to be discussed, directly or indirectly, referred to or illustrated with or without recognition within the presentation.



Supplement Use

- 70% of athletes in the Athens Summer Olympic Games
- 1 million American adolescents have taken a performance-enhancing substance



Goldman dilemma

- Would take a drug that guaranteed you a gold medal but would also kill you within five years?
- Elite Athlete > 50% yes
- General Population 0.8% yes
- Would I???
– Sure if I was 85



Elite athlete are different!!!

Problems

- \$ 20 Billion Dollar Industry



- Dietary Supplement and Health Act of 1994

- To improve the health status of the people of the United States
- Help constrain runaway health care spending (sic!)
- Clarify that dietary supplements are **NOT** drugs
- Burden of proof is on the FDA to prove that a product is unsafe before removal
- Establish labeling requirements

Supplement Definition

- A product intended to supplement the diet by increasing total dietary intake of one of the following: vitamin, mineral, herb or botanical, amino acid, another dietary substance
- Is not represented as a conventional food
- Is labeled as a dietary supplement



Dietary Supplement Myths

- It's Natural
- Supplements are not drugs
- Supplements are safer than pharmaceuticals
- Nicotine
- THC
- Heroin
- Cocaine
- Digoxin
- Many types of poisonous mushrooms



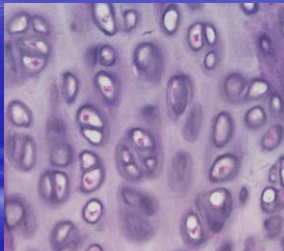
Problem??

- 12 different supplements (Green 2001)
 - 11 contained less than the stated amount
 - 1 had 177% of the stated amount
 - 2 contained none of the stated ingredients
 - 1 contained 10 mg of testosterone.
- Consumer Reports
 - July 2010
 - Test 15 common protein supplements
 - Low to moderate levels of arsenic, cadmium, lead, and mercury



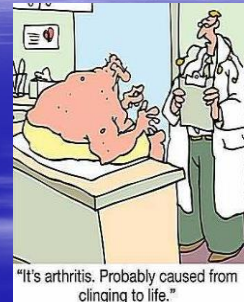
Supplements for OA Basic Science

- Hyaline (articular) cartilage
 - low-friction, wear-resistance tissue that bears and distributes load.
 - No innervations
 - No blood supply
 - Low metabolic rate



Basic Science

- Hyaline (articular) cartilage
 - Water
 - type II collagen,
 - Large aggregating proteoglycans, and chondrocytes.
- 2 types of glycosaminoglycans (GAG)
 - chondroitin sulfate and keratin sulfate
 - linked to hyaluronic acid



Supplement recommendation

- Dose it work?
- Is it safe?
- What is the cost?
 - Walletectomy



Glucosamine

- water-soluble amino monosaccharide
- cytokine-mediated pathways regulating inflammation, cartilage degradation, and immune responses
- precursor of glycosaminoglycans
- May promote glycosaminoglycan synthesis and/or reduce degradation
- substrate for new chondroitin sulfate synthesis

Chondroitin

- sulfated glycosaminoglycan
- Provides resistance to compression
- Both structural and regulatory
- Decrease cartilage degradation
- Provides base structural integrity
- Anti-inflammatory and immunomodulatory



Glucosamine Evidence In vitro

- the addition of glucosamine to chondrocyte cultures
 - increases aggrecan synthesis
 - anti-inflammatory effect, collectively reducing the catabolic protease effect
- Increases core protein synthesis
- Reduced metalloproteinase
- Interferes with IL-1 stimulation of Prostaglandin E
 - Inflammatory stimulator



Chondroitin Evidence In vitro

- Reduces IL-1–induced nuclear factor- κ B (NF- κ B) translocation in chondrocytes.
 - NF- κ B initiates pro-inflammatory genes
- Reduces expression of proinflammatory enzymes and molecules
 - phospholipase A2
 - cyclo-oxygenase-2
 - tumor necrosis factor
 - IL-1 and IL-8
 - metalloproteinase
 - prostaglandin E2



Glucosamine/Chondroitin Evidence Humans

- GAIT trial
 - N=1500
 - Glucosamine
 - Chondroitin
 - Both
 - Celebrex
 - Placebo
- Outcomes
 - Overall no benefit
 - Subset with moderate to severe knee pain did improve with combination



Glucosamine/Chondroitin Evidence Humans

- Cochrane Review
 - Some evidence glucosamine and to a lesser extent chondroitin improve pain and function
- Glucosamine
 - Rotta Brand (pharma grade) better than non-Rotta preparations
- Chondroitin
 - Pharmaceutical grade seems to provide some benefit



Dosage and side effects

- Glucosamine
 - 1500 mg day
 - 20% oral bioavailability
- Chondroitin
 - 1200mg day
 - 24% oral bioavailability
- Adverse effects
 - Nausea
 - Abdominal pain
 - Diarrhea
 - Others
 - All rates similar to placebo in most cases
- Some concern with glucose control in diabetics
 - Recent review found no issues



Nothing is ever without harm

- Int J Clin Pharmacol Ther. 2013 Mar;51(3):219-23. doi: 10.5414/CP201835.
- Drug-induced acute liver injury mimicking autoimmune hepatitis after intake of dietary supplements containing glucosamine and chondroitin sulfate



Other benefits?

- VITamins And Lifestyle (VITAL) study
 - glucosamine + chondroitin
 - on 4+ days/week for 3+ years
- reduced risk of colorectal cancer (CRC) after 5 years of follow-up.



MSM (METHYLSULFONYLMETHANE)

- organic mineral sulfur that is found in milk, vegetables, fish, and grains
- byproduct of dimethyl sulfoxide (DMSO)
- Promoted to
 - Rebuild cartilage
 - Anti-inflammatory
 - Help pain and function
- Side effects
 - GI upset
 - Diarrhea
 - Does not seem to have the garlic odor that DMSO creates



MSM Trials

- 3000mg BID x 12 weeks
 - No decrease in systemic inflammatory marker
 - Decrease knee pain
- 500mg TID ± glucosamine 500mg TID
 - Improvement in signs and symptoms of OA
 - Better in combination



Hyaluronan (HA), or hyaluronic acid

- GAG
- Viscoelastic biomechanical properties of synovial fluid
- Regulatory function
- orally administered HA has been shown to be absorbed, used, and taken up by joint tissue
- Human data
- Pilot trials of 50mg-100mg
- Improved physical function and pain over 4-8 weeks



S-Adenosyl-Methionine (SAM)

- activated form of the amino acid methionine
- precursor of glutathione
- protects synovial cells by reversing glutathione depletion
 - supporting levels of an important internal antioxidant enzyme glutathione peroxidase
- In Vitro
 - increases the chondroproliferation and proteoglycans synthesis



S-Adenosyl-Methionine (SAM)

- Human Evidence
- 3 trials SAM compared favorable to NSAIDS
- Dose
 - 800-1600mg day
- May be activating for patients on psychotropic drugs



Avocado Soybean Unsaponifiables- ASU

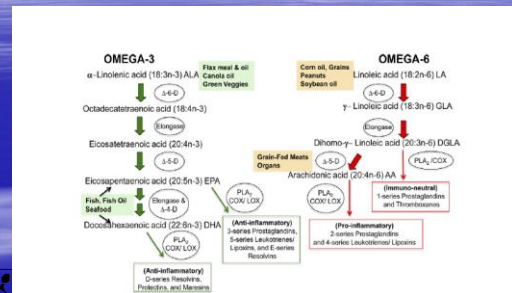
- natural vegetable extract made from avocado and soybean oils.
- Usual dose 300mg day
- Believed to slow cartilage breakdown by an anti-inflammatory effect
- In vitro stimulated collagen synthesis
- Human Evidence
 - Cochrane review
 - 300mg day doses
 - Improve both knee and hip pain in OA
 - Knee > Hip
 - Need 12 week trial

Fatty Acids

- Polyunsaturated FA (PUFA)
 - n-3
 - linolenic acid [ALA]
 - eicosapentaenoic acid (EPA)
 - omega-3 (an n-3 PUFA)
 - is found in canola oils, flaxseeds, walnuts, and fish oils,
 - n-6
 - linoleic acid [LA]
 - arachidonic acid [AA]
 - found in safflower, corn, soybean, and sunflower



Fatty Acids



Fatty Acids

- Evidence for Fish Oil
 - RA
 - Multiple trials show decrease in pain and improved joint function
 - OA
 - No human data
 - In vitro
 - Inhibits chondrocyte derived catabolic enzymes thought to play a role in OA
- OA- Animal
 - Guniea pig model
 - Diet rich in n-3
 - Improved biochemical markers of OA
 - matrix
 - metalloproteinase (MMP)-2
 - collagen cross-links
 - denatured type II collagen
 - glycosaminoglycan content
 - subchondral bone density

Fish Oil

- Rizzo et al JAMA 2012
- "omega-3 PUFA supplementation was not associated with a lower risk of all-cause mortality, cardiac death, sudden death, myocardial infarction, or stroke based on relative and absolute measures of association."

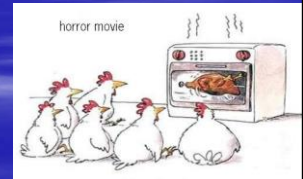


Collagen Preparations

- undenatured type II collagen
 - Improved biomarkers of OA compared to glucosamine and chondroitin in animal studies
 - Human studies show increased joint mobility, improves pain and functional status
- Mechanism
 - T cell re-education
 - Exposure of gut T-cells
 - Decrease immune response
 - may decrease targeted amplification of the immune response toward exposed type II collagen within the ECM of articular cartilage
- Dose
 - 40mg day
- Adverse Effects
 - minimal



- hydrolyzed collagen products
 - provide building blocks of the macromolecular components to support the matrix of cartilage
 - chicken-sternal cartilage
- In vivo
 - Improvement in pain
- Dose
 - 10g/day
- Side Effects
- Minimal
- In vitro
 - Dose dependent stimulation of chondrocytes



Vitamin D

- Fat-soluble Vitamin
- Primarily produced in the skin
 - Exposure to uv B radiation
 - Melanin and sunblock (SPF 15) can block up to 99% of production
- Small amount obtained through dietary sources
- Secosteroid hormone
 - D3 converted to 25-hydroxyvitamin D in the liver
 - Converted to active form- calcitriol in the kidney
 - Other vitamins are generally cofactors for enzymatic reactions



Vitamin D

- Calcitriol
 - Signals gene transcription
 - Regulates
 - Bones/calcium
 - Muscle
 - Skeletal/cardiac
 - Immune system
 - Anti-cancer activity



Vitamin D

- Felson et al 2007
 - Longitudinal
 - N = 715
 - No correlation between Vit D levels and radiographic progression of OA
- Ding et al 2009
 - Sunlight exposure and Vit D levels correlate with decrease cartilage loss
- McAlindon et al JAMA 2013
 - 2-year RCT, placebo, double blind
 - n= 146
 - symptomatic knee OA
 - Placebo or Vit D
 - Vit D increased to > 36ng/ml
 - WOMAC and cartilage loss on MRI
 - No reduction in pain or cartilage volume loss



Other Vitamins

- Vit C
 - Antioxidant
 - Coenzyme in collagen fibril cross linking
 - Weak evidence in humans for use in OA
 - McAlindon et al
 - Framingham OA cohort
 - > 75 mg day
 - Reduced risk of cartilage loss, knee pain and OA
- Vit E
 - Free radical scavenger
 - 200 IU
 - Small trial
 - Decrease pain and stiffness in OA



Others

Curcumin

- diferuloylmethane aromatic component of the Indian spice turmeric
- anti-inflammatory compound
 - inhibits both COX-2 and 5-LOX enzyme activity
 - 1 small study shows equal to ibuprofen
- Dose
 - 2-10 g/day
 - Adverse
 - Watch in antiplatelet/anticoagulated patients

Ginger

- suppressed TNF- and inhibited COX-2-mediated synthesis of proinflammatory mediators
- 2 placebo controlled trials
- Improvement in pain and function



Flavocoxid

- FDA prescription medical food
- Some evidence effective for OA pain
 - 500mg BID
 - COX and 5-LOX inhibition of arachidonic acid metabolism

- Acute liver injury due to flavocoxid (Limbrel), a medical food for osteoarthritis: a case series, Arch of Internal Medicine 2012



Deer and Elk Velvet antler (VA)

- is a dietary supplement made from the antlers of deer or elk
 - surgically removed from a live animal under anaesthetic.

Singh admits using deer antler spray, says he was unaware it was banned



Claims

- Improves immune system functioning;
- Improves athletic performance and strength; ↑ IGF-1
- Improves muscle recovery after exercise;
- Reduces negative effects of stress;
- Enhances sexual functioning for both men and women;
- Promotes rapid recovery from illness;
- Has anti-cancer and anti-inflammatory properties.



WADA OKAY
WITH IT

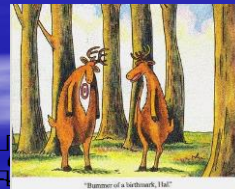


Velvet Antler

- Edleman 2000 J of Rheum
 - RCT 2 arms
 - N = 54
 - VAS/WOMAC scores
- Symptomatic relief of symptoms

- Industry sponsored
- Underpowered
- Randomization not completely discussed

- Potential but needs further study



What should we recommend?

Tier 1 – benefits/cost/evidence outweigh risk	Dose	Notes	Cost/month*
Glucosamine Sulfate (pharma)	1500mg 1 x day	Trial for 12 weeks	Non-Rotta ≈ \$10-15 Rotta ≈ \$30
Chondroitin Sulfate (pharma)	1200 mg 1 x day	Trial for 12 weeks	≈ 18-20
Vitamin D3	2000- 4000 IU x day	Use D3 not D2 Consider level measurement	≈ \$2-3



What should we recommend?

Tier 2 – benefits/evidence limited Low harm/cost	Dose	Notes	Cost/month*
Vitamin C	250mg-500mg x day		≈ \$2
MSM	1-3 grams 2 x day	May be better in combo with glucosamine	≈ \$5-10
HA	50-100mg x day		≈ \$10-12
FA	2-4 grams x day		≈ \$2-5



What should we recommend?

Tier 3 – benefits/evidence limited/unknown possible harm/cost	Dose	Notes	Cost/month*
SamE	400mg-600mg x day	Consider Vit B supplementation-homocysteinemia Avoid in pts on psychotropic medication	≈ \$20-30
ASU	300-600mg x day	Early evidence promising	≈ \$15-20
undenatured type II collagen/hydrolyzed	40mg x day/ 2-10grams		≈ \$5-15
Ginger	1 gram x day		≈ \$1-2
Curcumin	2-10 grams/day	Cautious in anti-platelet/anticoagulated patients	≈\$5-6

What should we recommend?

Tier 4 –Evidence not effective harm/cost	Dose	Notes	Cost/month*
Flavocoxid		Liver toxicity	≈ \$20-30
Velvet Antler	varies	limited	≈ \$60-80



Recommendations

- Stepwise fashion
- Tier 1
 - Glucosamine/chondroitin (Vitamin D for all)
 - Add others based on failure or results
- Tier 2 for patients who fail Tier 1 or partial response
- Discuss Tier 3 only in selected patients



Conclusion

- Mixed or early data on most supplements
- Not all supplements are benign



Thank you



Selected References

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