Supplements in Osteoarthritis
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DISCLOSURE
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

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 metalloprotienease
  - Interferes with IL-1 stimulation of Prostaglandin E1

Glucosamine Evidence

- In vitro
  - Reduces IL-1–induced nuclear factor-B (NF-B) translocation in chondrocytes.
    - NF-B initiates pro-inflammatory genes
  - Reduces expression of proinflammatory enzymes and molecules
    - Phospholipase A2
    - Cyclooxygenase-2
    - Tumor necrosis factor
    - IL-1 and IL-8
    - Metallomatrix proteinase
    - Prostaglandin E2

Glucosamine/Chondroitin Evidence

- In vitro
  - Reduces IL-1–induced nuclear factor-B (NF-B) translocation in chondrocytes.
    - NF-B initiates pro-inflammatory genes
  - Reduces expression of proinflammatory enzymes and molecules
    - Phospholipase A2
    - Cyclooxygenase-2
    - Tumor necrosis factor
    - IL-1 and IL-8
    - Metallomatrix proteinase
    - 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
    - Doesn’t provide some benefit

Dosage and side effects

- Glucosamine
  - 1500 mg day
  - 20% oral bioavailability
  - Adverse effects
    - Nausea
    - Abdominal pain
    - Diarrhea
    - Others
    - All rates similar to placebo in most cases

- Chondroitin
  - 1200 mg day
  - 24% oral bioavailability
  - Some concern with glucose control in diabetics
  - Recent review found no issues
Nothing is ever without harm

- Drug-induced acute liver injury mimicking autoimmune hepatitis after intake of dietary supplements containing glucosamine and chondroitin sulfate

"Everything’s a tradeoff — now that I can walk upright, I can’t wiggle my ears any more."

Other benefits?

- VITamins And Lifestyle (VITAL) study
  - glucosamine + chondroitin
  - on 4+ days/week for 3+ years
  - reduced risk of colorectal cancer (CRC) after 8 years of follow-up

MSM (METHYL SULFONYLMETHANE)

- 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 order 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
- Regulator 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
- Supports levels of an important internal antioxidant enzyme glutathione peroxidase

- In Vitro
  - Increases the chondroproliferation and proteoglycan 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**

- **Human Evidence**
  - 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

**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
    - Arachidonic acid [AA]
    - Found in safflower, corn, soybean, and sunflower

**Fish Oil**

- **Evidence for Fish Oil**
  - RA
    - Multiple trials show decrease in pain and improved joint function
  - OA
    - No human data
    - In vitro
      - Anti-inflammatory effects on cartilage enzymes thought to play a role in OA
  - **OA - Animal**
    - Guinea pig model
    - Diet rich in n-3
    - Improved biochemical markers of OA

- **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 chondrotin in animal studies
  - Human studies show increased joint mobility, improves pain and functional status

- **Mechanism**
  - T-cell re-eduaction
  - 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 vitro**
  - Dose dependent stimulation of chondrocytes

- **In Vivo**
  - Improvement in pain
  - Dose - 10g/day

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 - calcitrol in the kidney
  - Other vitamins are generally cofactors for enzymatic reactions

- **Calcitrol**
  - Signals gene transcription
  - Regulates
    - Bones/calciutum
    - Muscle
    - Skeletal/cardiac
    - Immune system
    - Anti-Cancer activity

Vitamin D

- **Felson et all 2007**
  - Longitudinal
    - N = 715
    - No correlation between Vit. D levels and radiographic progression of OA

- **Ding et all 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
    - 75mg 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**
  - Dietary herbal aromatic component of the Indian spice turmeric
  - Anti-inflammatory compound
    - Inhibits both COX-2 and 5-LOX enzyme activity
    - 1 small study showed equal to ibuprofen
  - Dose
    - 2-10 g/day
  - Adverse: 
    - Viral/myocardial/anticoagulant 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
    - 500 mg 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

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

**Velvet Antler**

- Edelman 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?**

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Benefits/Cost/Evidence Overweigh Risk</th>
<th>Dose</th>
<th>Notes</th>
<th>Cost/month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucosamine Sulfate (pharma)</td>
<td>1500 mg 1 x day</td>
<td>Trial for 12 weeks</td>
<td>Non-Rotta ≈ $10-15; Rotta ≈ $30</td>
<td></td>
</tr>
<tr>
<td>Chondroitin Sulfate (pharma)</td>
<td>1200 mg 1 x day</td>
<td>Trial for 12 weeks</td>
<td>≈ $18-20</td>
<td></td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>2000-4000 IU x day</td>
<td>Use D3 not D2</td>
<td>Consider level measurement</td>
<td>≈ $2-3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tier 2</th>
<th>Benefits/Evidence Limited Low Harm Cost</th>
<th>Dose</th>
<th>Notes</th>
<th>Cost/month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td>250 mg-500 mg x day</td>
<td>May be better in combo with glucosamine</td>
<td>≈ $2</td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td>1-3 grams 2 x day</td>
<td>May be better in combo with glucosamine</td>
<td>≈ $5-10</td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td>50-100 mg x day</td>
<td></td>
<td>≈ $10-12</td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>2-4 grams x day</td>
<td></td>
<td>≈ $2-5</td>
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</tbody>
</table>
What should we recommend?

<table>
<thead>
<tr>
<th>Tier 3 – benefits/evidence limited/unknown possible harm/cost</th>
<th>Dose</th>
<th>Notes</th>
<th>Cost/month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAME 400mg-600mg x day</td>
<td>Consider VIT B supplementation-homocysteinemia Avoid in pts on psychiatric medication</td>
<td>= $20-30</td>
<td></td>
</tr>
<tr>
<td>ASU 300-600mg x day</td>
<td>Early evidence promising</td>
<td>= $15-20</td>
<td></td>
</tr>
<tr>
<td>Undenatured type II collagen/hydrolyzed 40mg x day 2-10grams</td>
<td>Early evidence promising</td>
<td>= $5-15</td>
<td></td>
</tr>
<tr>
<td>Ginger 1 gram x day</td>
<td>Avoid in pts on psychotrophic medication</td>
<td>= $1-2</td>
<td></td>
</tr>
<tr>
<td>Curcumin 2-10 grams/day</td>
<td>Caution in anti platelet/anticoagulated patients</td>
<td>= $5-6</td>
<td></td>
</tr>
</tbody>
</table>

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

Selected References


Thank you