Dr. Wayne McIlwraith

Barbara Cox Anthony Endowed University Chair in Orthopaedics, Orthopaedic Research Center

Colorado State University

Nutraceuticals (Oral Joint Supplements)

Wayne McIlwraith BVSc, PhD, DACVS, DACVSMR

University Distinguished Professor

Barbara Cox Anthony Chair in Orthopaedics

Director of Orthopaedic Research Center

Colorado State University

Seventh Welfare and Safety of the Racehorse Summit

Keeneland, Lexington, KY

June 18, 2016

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Grayson-Jockey Club Research Foundation, Inc.

Welfare and Safety of the Racehorse Summit

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Disclosures

- Consultant for Arthrex & PulseVet
- Shareholder in Advanced Regenerative Therapies (ART)
- Director ANZAC
- Research funding from
  - IDEXX
  - Bayer
  - Luitpold
  - Arthrex
  - Orthogen
  - PulseVet
  - VetStem
  - Merial
- Other research funded by independent agencies

Osteoarthritis (OA)

- Single most common lameness in horses
  - Clegg & Booth *Practice* 2000
- Horse population in US estimated $7.3 million & therefore millions of horse have this debilitating condition
- OA similarly important in humans affecting at least 20 million Americans with incidence expected to double over next in next 2 decades

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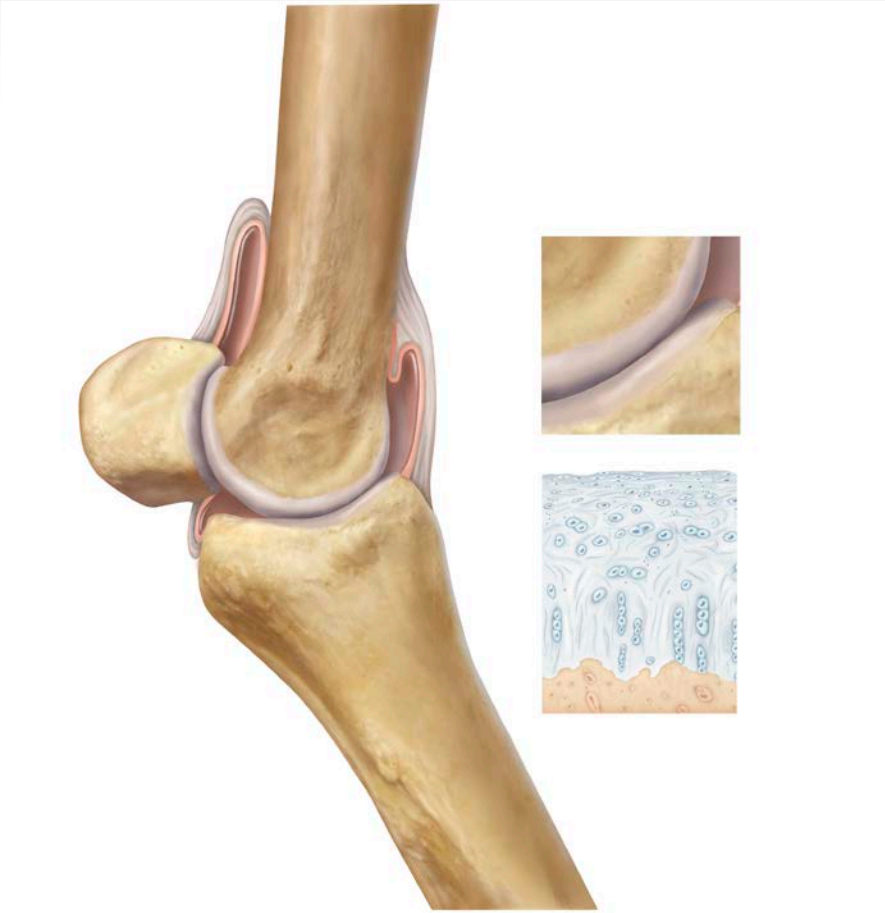
Osteoarthritis (OA)

- Oral joint supplements (OJSs) are a common choice of clients and have been perceived as a benign treatment for OA in horses
- The high prevalence of OA combined with the lack of a definitive cure has probably contributed to the popularity of OJSs
- Side effects of NSAIDs & corticosteroids an argument as well

Stages of OA in a High Motion Joint

Normal Joint



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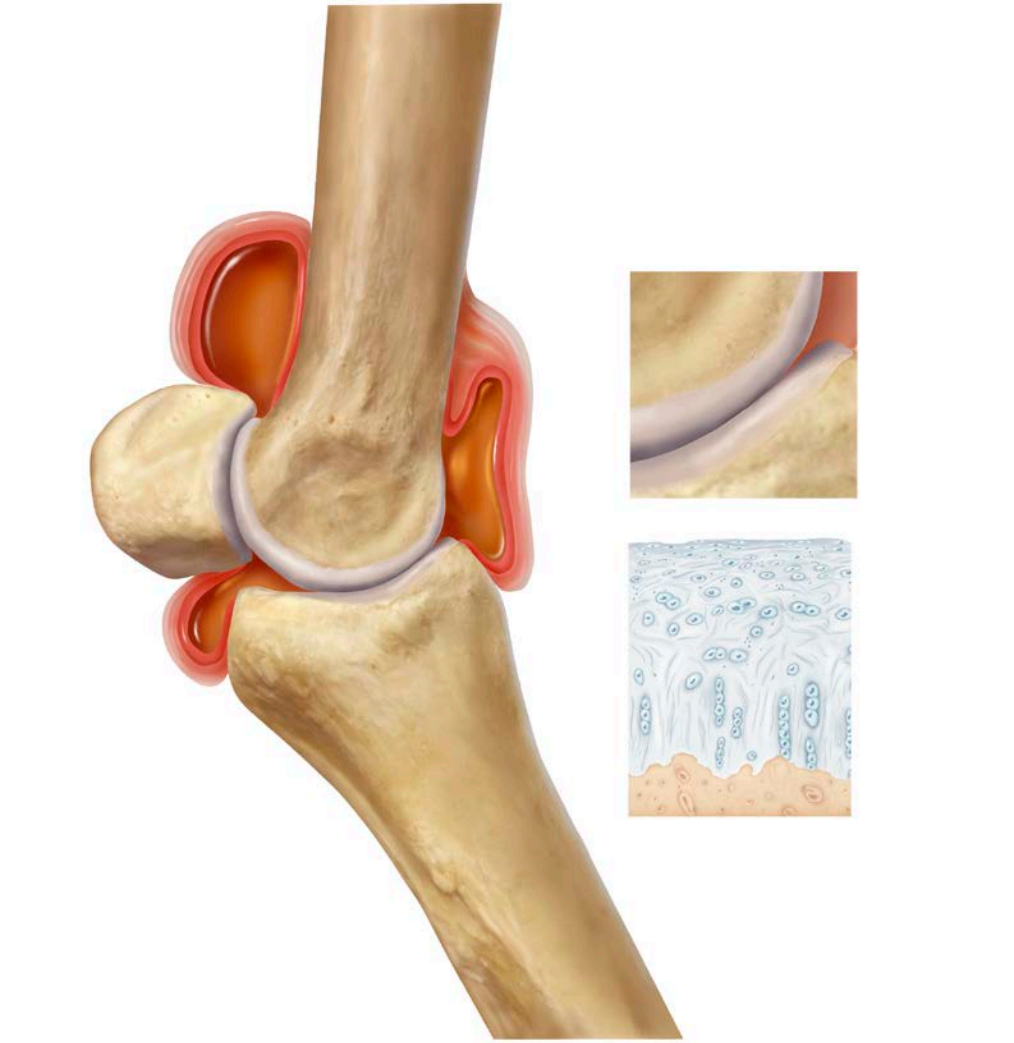
Stage 1 OA

- Synovitis and no morphologic change in articular cartilage



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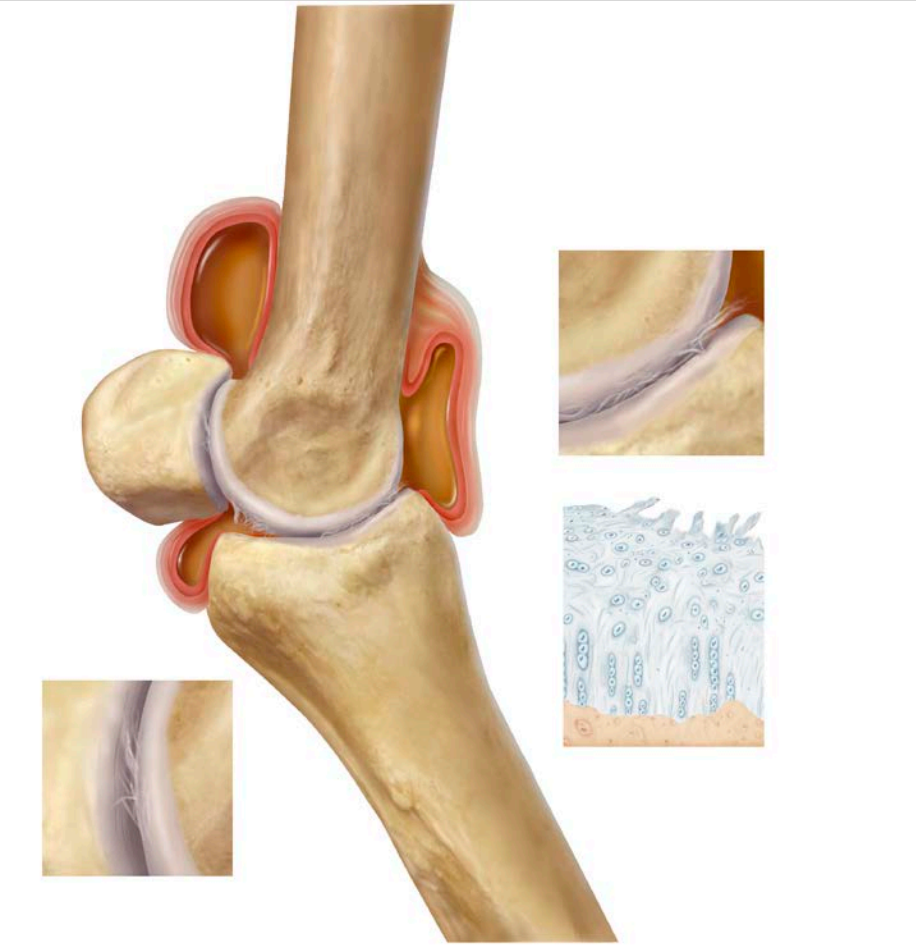
Stage 2 OA

- Synovitis less acute
- Morphologic damage in articular cartilage commencing



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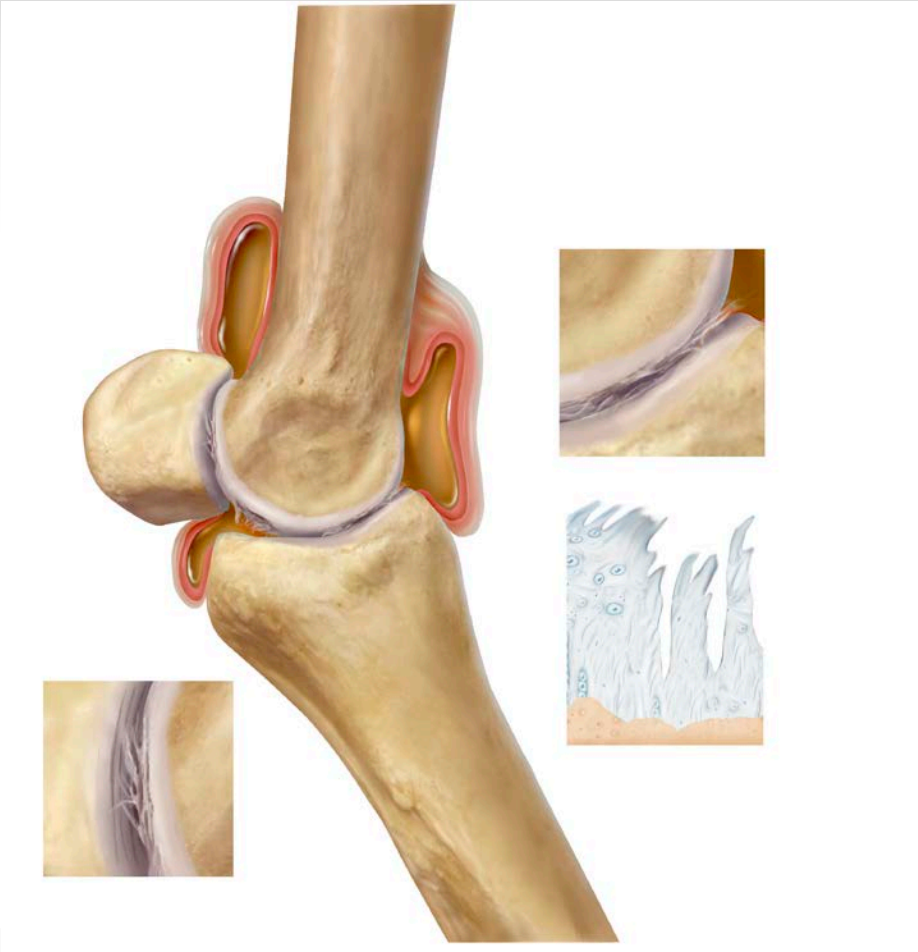
Stage 3 OA

- Synovitis chronic
- Morphologic damage in articular cartilage severe



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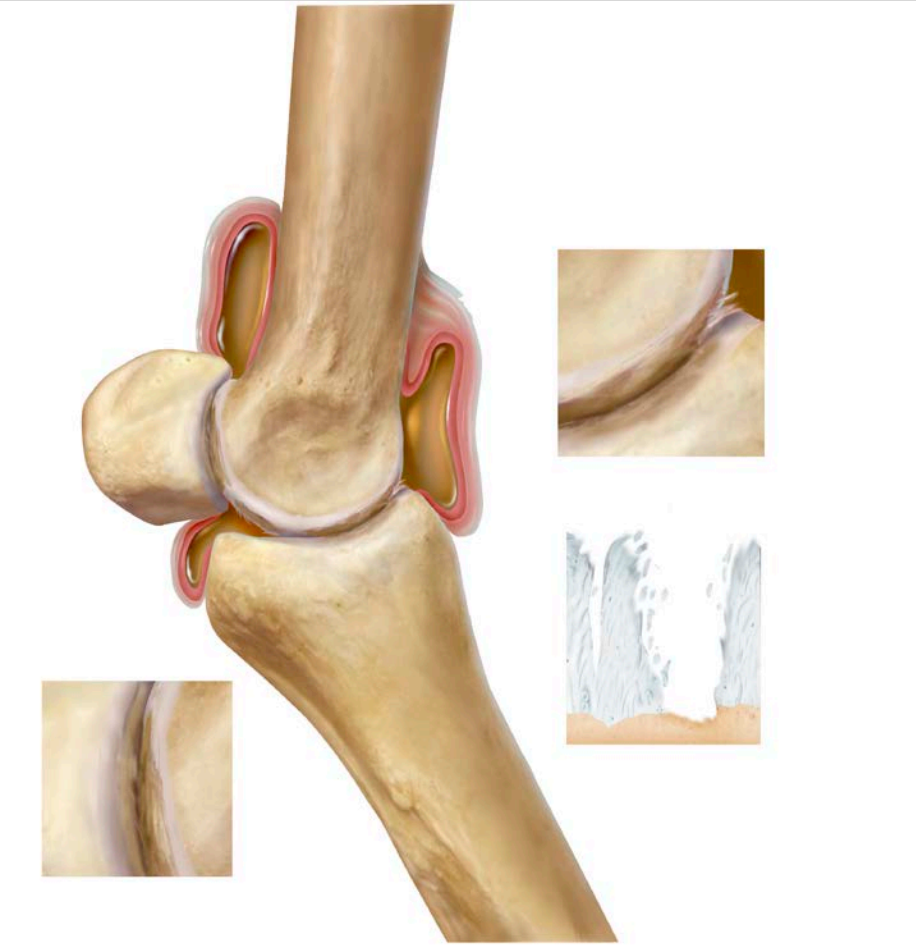
Stage 4 OA

- Synovitis chronic
- Full thickness loss of articular cartilage



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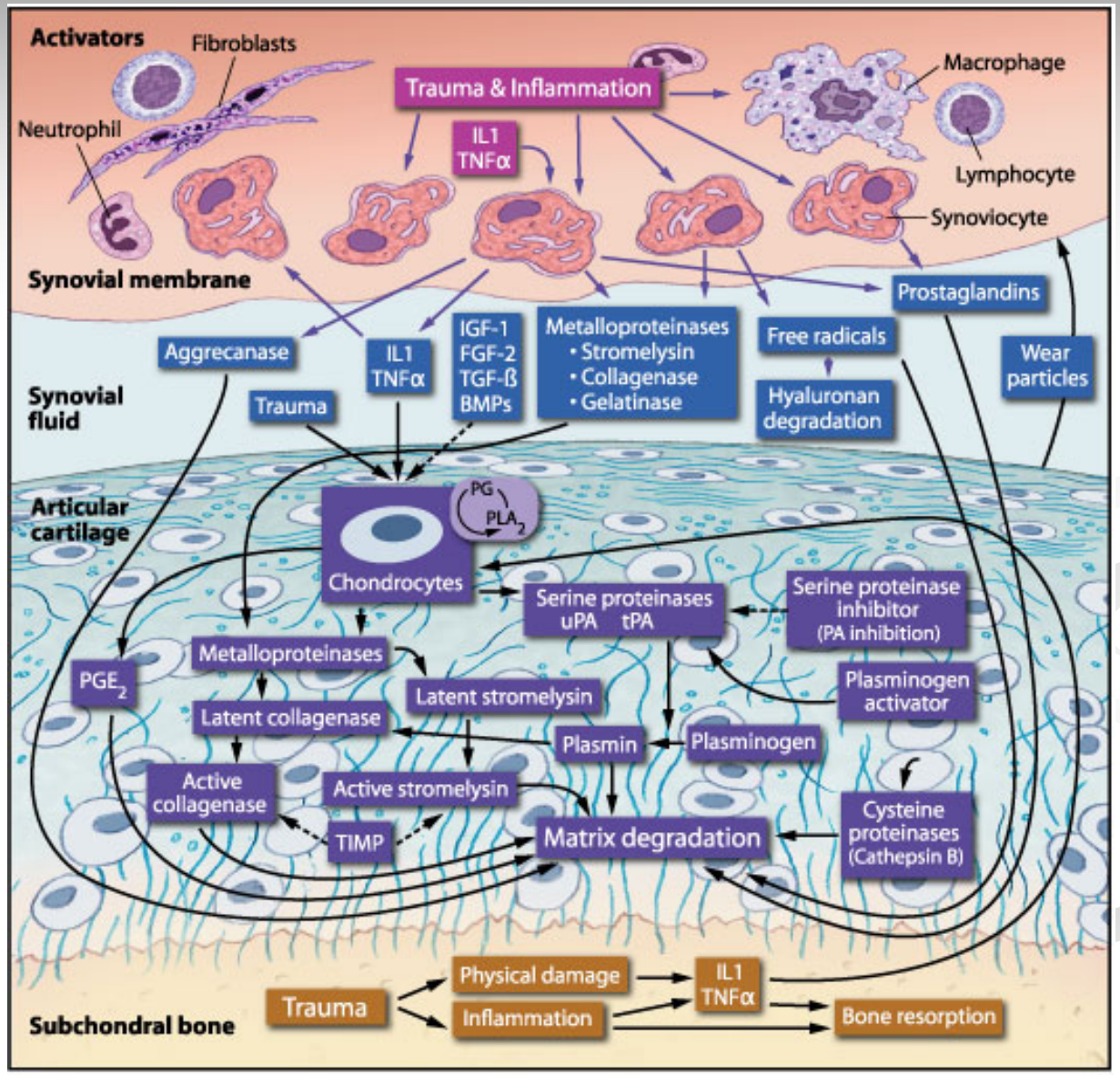
Factors Involved in Degradation of Articular Matrix



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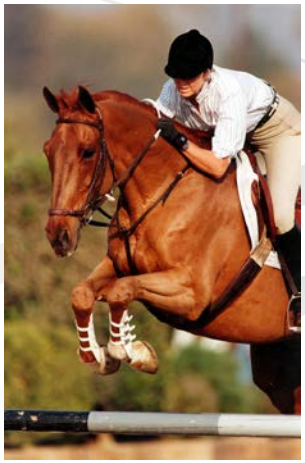
Goal of treatment in all traumatic joint entities

- Return the joint to normal as quickly as possible
- Prevent the occurrence or reduce the severity of OA **In other words:**
- Reduce pain and minimize progression of joint deterioration
  - **Symptom modifying OA Drugs (SMOADs)**
  - **Disease modifying OA drugs (DMOADs)**
- Timely removal of osteochondral fragments, fixation of IA fractures, accurate diagnosis of ligamentous & meniscal injuries & appropriate treatment of OCD entities are also critical treatments to prevent OA

We Evaluate Effectiveness of Treatments using Two Criteria with *in vivo* Studies

- Symptom modifying effects (SMOADs)
  - Improvement in clinical signs
- Disease modifying effects (DMOADs)
  - Proof that progressive OA disease is modified
- Ideally we want both but second is critical and valuable long term



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Treatments of Traumatic Arthritis & OA Evaluated in Controlled Studies

- Physical therapy and rehabilitation
- Extracorporeal shock wave therapy
- NSAIDs
- IA corticosteroids
- IA HA
- IV HA
- Oral HA
- IA PSGAG
- IM PSGAG
- IM Pentosan polysulfate
- **Oral joint supplements (nutraceuticals)**
- Anti-cytokine therapy (protein or gene therapy)
- Platelet rich plasma
- Mesenchymal stem cells

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Nutraceuticals (Oral Joint Supplements)

- Where do they fit in all this?
  - Not usually prescribed specifically by a veterinarian
  - Common choice of clients & have been perceived as a benign treatment for OA in horses
    - Trumble TN.The use of nutraceuticals for osteoarthritis in horses. *North Am Vet Clin Equine Pract* 2005

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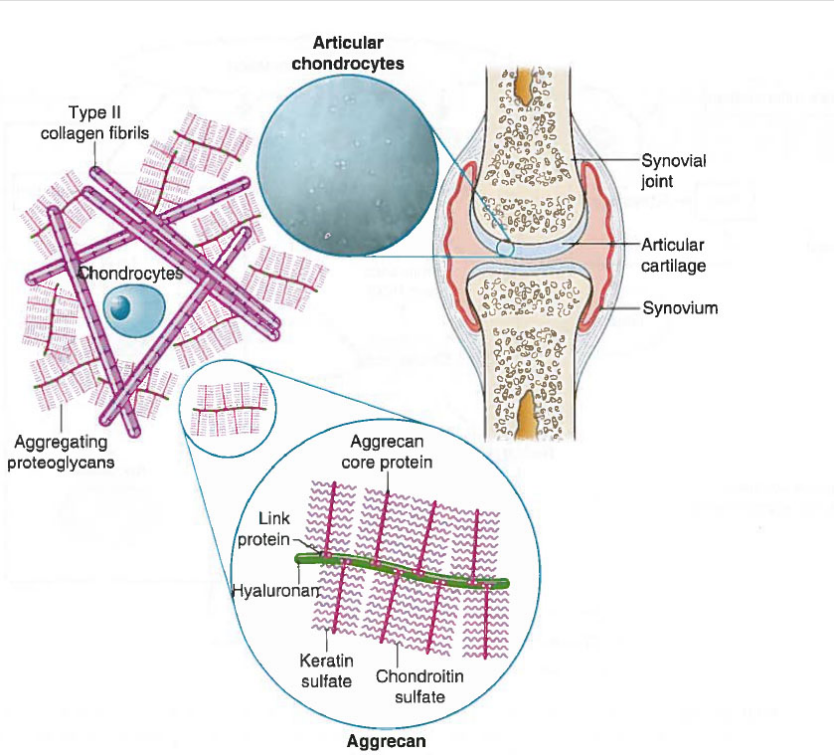
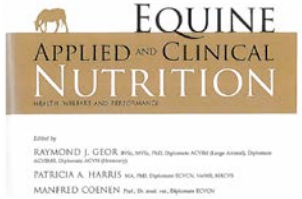
Critical Components of Articular Cartilage Also Need to be Maintained

- 'Joint maintenance' a common indicationType II collagen
- Extracellular matrix
  - Proteoglycans
  - Water



McIlwraith CW (2013) Oral joint supplements in the management of osteoarthritis In Geor, Harris & Coenen et al (eds) Equine Applied and Clinical Nutrition



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Oral Joint Supplements (OJSs)

- High prevalence of OA in combination with lack of definitive cure has probably contributed to popularity of OJSs
- Most popular types of nutritional supplements for horses (half of all equine supplements sold in US)
- Estimated that 49% of all horse owners use
  - Packaged Facts 2008 www.packaged facts.com/pet-supplements-market-c1641

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Indications for Oral Joint Supplements

- OJSs are fed to horses for one of two purposes:
  - To treat lame horses and make chronically unsound horses sound..this use is flawed because often the source of lameness is never diagnosed when the owner or trainer elects to use supplements without consulting a veterinarian
  - OR
  - To prevent/delay the development of joint problems..hard to prove/disprove but is basis for high use of im Adequan® & iv Legend® as well as OJSs

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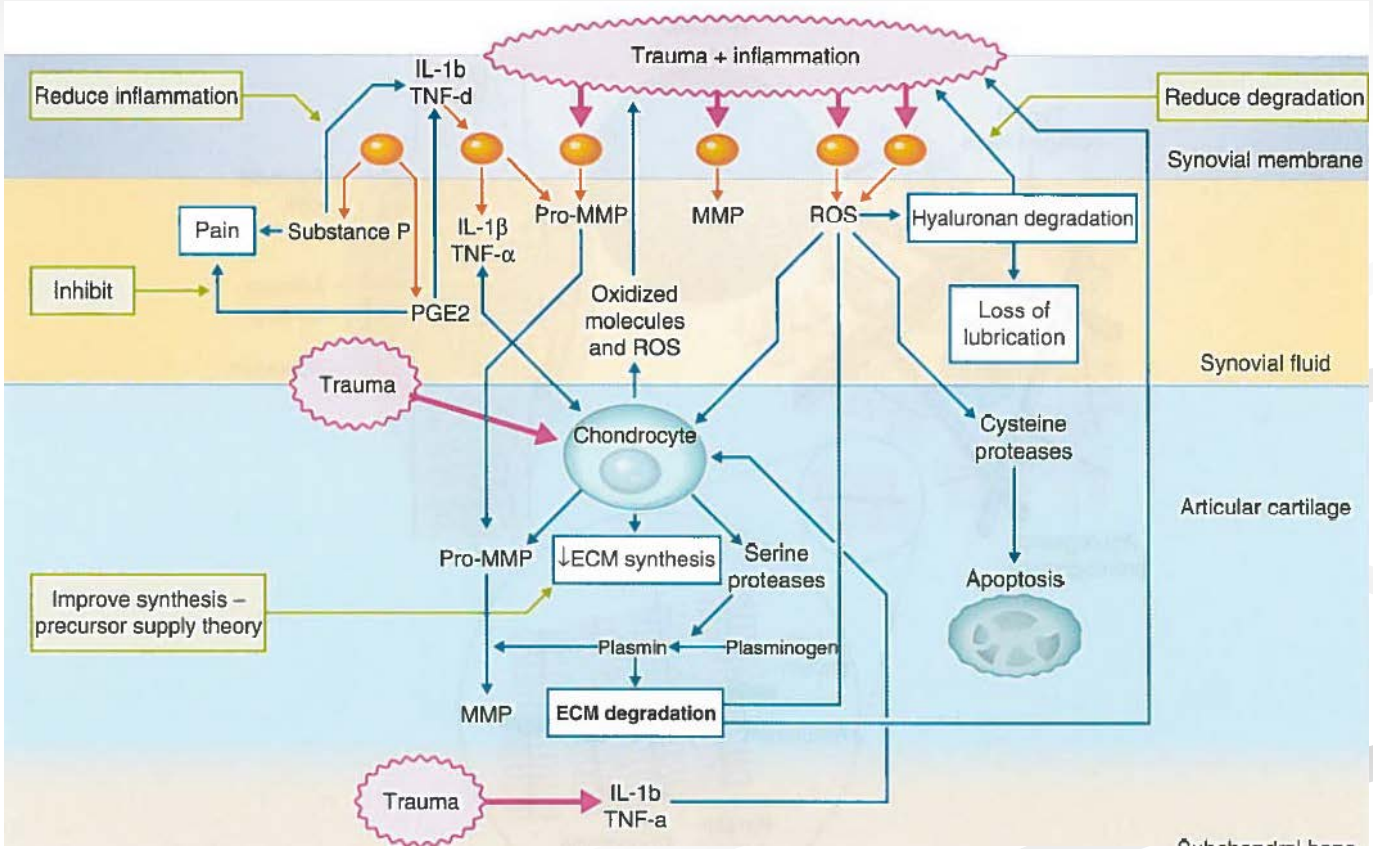
Mechanisms for development of OA & possible mechanisms of action for OJSs in mitigating these processes – mainly derived from in vitro data



McIlwraith CW (2013)

Types of Oral Joint Supplements

- Majority include glucosamine (GU) and/or chondroitin sulfate (CS) along with other added ingredients
- May also contain additional ingredients including manganese, vitamin C, hyaluronic acid or HA, polyunsaturated fatty acids (PUFAs), rare earth minerals, unsaponified avocado soy (ASU), green lipped muscle (Perna canaliculus), cetylmyristoleate, methylsulfonylmethane, & various herbs - with exception of last two (no good equine documentation) we will discuss these various products

Oral nutraceuticals-marketing with little control is a issue

- Inappropriate advertising is an issue
- Some FDA letters but 'joint formula' & 'promoting joint health' insinuate therapeutic effects

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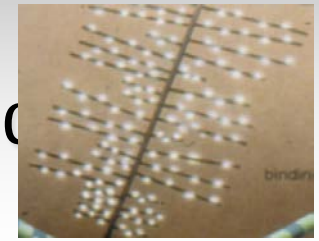
Oral Joint Supplements

- None of the oral supplements or oral nutraceuticals are licensed
- Most products include glucosamine and/or chondroitin sulfate along with other added ingredients
- Initial products for horse:
  - CS product from bovine trachea (Flex-Free®
  - Complex of GAGs and other nutrients from the sea mussel *Perna canaliculus* (SynoFlex®)
- Cosequin® - combination of glucosamine (GU), CS, manganese, and vitamin C
- Number of other products followed simulating Cosequin®

In vitro dose titration studies of GU & CS alone & in combination with equine cartilage explants



- Decreased GAG loss into medium with higher c of GU, CS and GU+CS
- Intermediate doses enhanced GAG synthesis and total cartilage GAG content
  - Dechant, Baxter, Frisbie et al *Equine Vet J* 2005

Effects of glucosamine hydrochloride and chondroitin sulphate, alone and in combination, on normal and interleukin-1 conditioned equine articular cartilage explant metabolism

J. E. DECHANT*, G. M. BAXTER, D. D. FRISBIE, G. W. TROTTER and C. W. McILWRAITH

Equine Orthopaedic Research Laboratory, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, Colorado 80523, USA.

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Same dosages tested on IL-1 conditioned explants

- No treatment effects for GU or CS alone
- Protective effect for GU+CS for total GAG release into the media
- How does it relate to concentrations achieved with oral administration?

Effects of glucosamine hydrochloride and chondroitin sulphate, alone and in combination, on normal and interleukin-1 conditioned equine articular cartilage explant metabolism

J. E. DECHANT*, G. M. BAXTER, D. D. FRISBIE, G. W. TROTTER and C. W. McILWRAITH

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What about absorption compared to in vitro levels that are efficacious?

- Chondroitin sulfate - yes - low molecular weight CS (0.80 kD) absorbed to a greater degree than GU; absorption may be influenced by MW
  - Du et al *Biopharm Drug Dispos* 2002
- Glucosamine - not in sufficient levels
  - Laverty et al *Arthritis Rheum* 2004
- Still does not prove effectiveness in the horse

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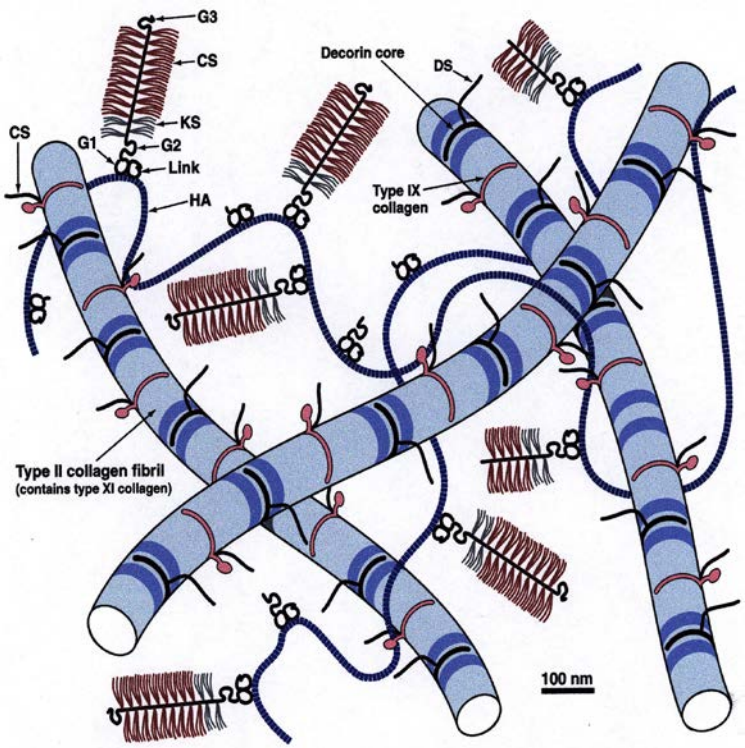
Serum GAG & HA levels Do Not Reflect Absorption as has been Claimed

- Both marker of inflammatory joint disease



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Clinical Trials

- In a review of 15 in vivo equine studies, authors signaled an encouraging trend: manufacturers of these products are investing in research, but most do not meet a quality standard that provided sufficient confidence in the results reported. Consequently, the overall level of evidence for in vivo demonstration of efficacy is weak.

706

EQUINE VETERINARY JOURNAL
Equine vet. J. (2009) **41** (7) 706-712
doi: 10.2746/042516409X424153

Review Article

Low quality of evidence for glucosamine-based nutraceuticals in equine joint disease: Review of *in vivo* studies

W. PEARSON* and **M. LINDINGER†**

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Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)

- Knee pain
  - Placebo
  - GS
  - CS
  - GS+ CS
  - Celecoxib
- 1583 randomized & 1258 (80%) completed study
  - No significant improvement in knee pain versus placebo was seen in supplement group but improvement with celecoxib
  - In subset with moderate to severe knee pain some improvement seen

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 23, 2006 VOL. 354 NO. 8

Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis

Daniel O. Clegg, M.D., Domenic J. Reda, Ph.D., Crystal L. Harris, Pharm.D., Marguerite A. Klein, M.S., James R. O'Dell, M.D., Michele M. Hooper, M.D., John D. Bradley, M.D., Clifton O. Bingham III, M.D., Michael H. Weisman, M.D., Christopher G. Jackson, M.D., Nancy E. Lane, M.D., John J. Cush, M.D., Larry W. Moreland, M.D., H. Ralph Schumacher, Jr., M.D., Chester V. Oddis, M.D., Frederick Wolfe, M.D., Jerry A. Molitor, M.D., David E. Yocum, M.D., Thomas J. Schnitzer, M.D., Daniel E. Furst, M.D., Allen D. Sawitzke, M.D., Helen Shi, M.S., Kenneth D. Brandt, M.D., Roland W. Moskowitz, M.D., and H. James Williams, M.D.

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Sasha's Blend

- NZ green-lipped mussel, shark cartilage, abalone & a lipid extract from *Biota orientalis* = Sasha's EQ Powder (SEO)
- Decreased IL-1βinduced PGE2 *in vitro*
- Evaluated by feeding horses SEO at different doses with placebo group & injected one carpus with IL-1β& one with saline.
- SEO significantly inhibited increased PGE2 & GAG levels with IL-1β
  - Pearson et al Mol.Nutr.Food.Res. 2007;51:1020-1030

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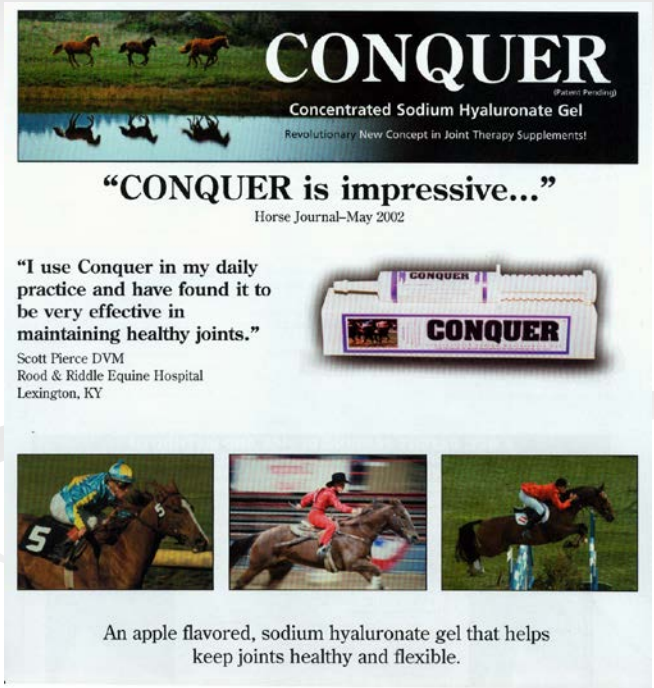
Oral Hyaluronan

- Anecdotal support for effectiveness
- A number of products (two developed by veterinarians)
  - Conquer®
  - Lubrisyn®
- Anecdotal reports of benefit in OA



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Evidence for efficacy of oral hyaluronan

- Oral HA (Conquer™) given after arthroscopic surgery for tarsocrural OCD
  - 27 joints (24 yearlings) treated with 100 mg orally for 30 days postop
  - 30 joints (24 yearlings) treated with placebo orally for 30 days
  - Blinded examiner scored effusion at 30 days (grade 0-5)
- Mean 30 day effusion score treated group 0.67 in treated group and 2.05 in placebo group (p<0001)
  - Bergin et al Equine Vet J 2006; 38:375-378

EQUINE VETERINARY JOURNAL
Equine vet. J. (2006) **38** (4) 375-378

Oral hyaluronan gel reduces post operative tarsocrural effusion in the yearling Thoroughbred

B. J. BERGIN*, S. W. PIERCE, L. R. BRAMLAGE and A. STROMBERG†

Rood and Riddle Equine Hospital, PO Box 12070, Lexington, Kentucky, 40580-2070, USA. †Department of Statistics, University of Kentucky, Lexington, Kentucky 40506-0027, USA.

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Extract of Green-lipped Mussel (*Perna canaliculus*)

- Randomized, double-blinded placebo controlled study in horses with clinical cases [chronic fetlock lameness (OA)]
- 19 treated & 20 placebo – 56 days
- Significant reduction in severity of lameness ($p<0.001$), reduced joint pain ($p<0.014$), & improved response to joint flexion ($p<0.001$)

nary Journal ISSN 0425-1644
DOI: 10.1111/j.2042-3306.2011.00455.x

A randomised, double-blinded, placebo-controlled study on the efficacy of a unique extract of green-lipped mussel (*Perna canaliculus*) in horses with chronic fetlock lameness attributed to osteoarthritis

J. CAYZER*, D. HEDDERLEY† and S. GRAY‡

Estendart Ltd, Massey University, Private Bag, Palmerston North, New Zealand; †The NZ Institute for Plant and Food Research Ltd, Food Industry Science Centre, Fitzherbert Science Centre, Private Bag, Palmerston North, New Zealand; and ‡Samantha Gray Consulting, Auckland, New Zealand.

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Avocado Soy Unsaponified (ASU)

- Vetoquinol ASU studied in equine OA model
- First controlled equine study demonstrating a positive effect with an oral nutraceutical ➔disease-modifying effects
- Controlled studies in humans also positive

Evaluation of avocado and soybean unsaponifiable extracts for treatment of horses with experimentally induced osteoarthritis

Christopher E. Kawcak, DVM, PhD; David D. Frisbie, DVM, PhD;
C. Wayne McIlwraith, BVSc, PhD; Natasha M. Werpy, DVM; Richard D. Park, DVM, PhD

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Equine Study with ASU (Luxovan®)

- Two treatment groups (8 horses in each)
- Osteochondral fragment model
- Gp 1 : ASU with sweet feed. Administered orally once a day from day 0-72
- Gp 2 : Sweet feed. Administered orally once a day from day 0-72

Evaluation of avocado and soybean unsaponifiable extracts for treatment of horses with experimentally induced osteoarthritis

Christopher E. Kawcak, DVM, PhD; David D. Frisbie, DVM, PhD;
C. Wayne McIlwraith, BVSc, PhD; Natasha M. Werpy, DVM; Richard D. Park, DVM, PhD

AJVR

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Synovitis-OA

16 Horses

8 Horses

No Chip

Chip

ASU

ASU

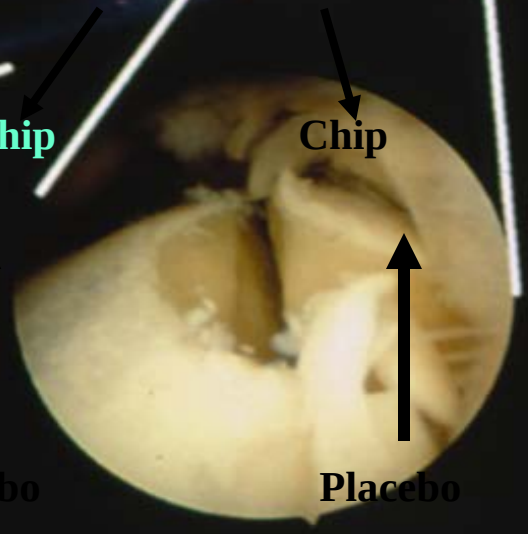
8 Horses

No Chip

Chip

Placebo

Placebo



Outcome Parameters

- Lameness - pre- & post-flexion every 2 weeks
- Radiographs prior to surgery & at study conclusions
  - Changes in subchondral bone & osteophytosis
- Synovial fluid once a week
- Serum once a week
- Treadmill exercise days 15 - 72 (5 days a week : 2 minutes trot, 2 minutes gallop, 2 minutes trot)
- Gross necropsy
- Histopathology
  - Synovial membrane
  - Articular cartilage
- Articular cartilage biochemistry
  - GAG content
  - GAG synthesis

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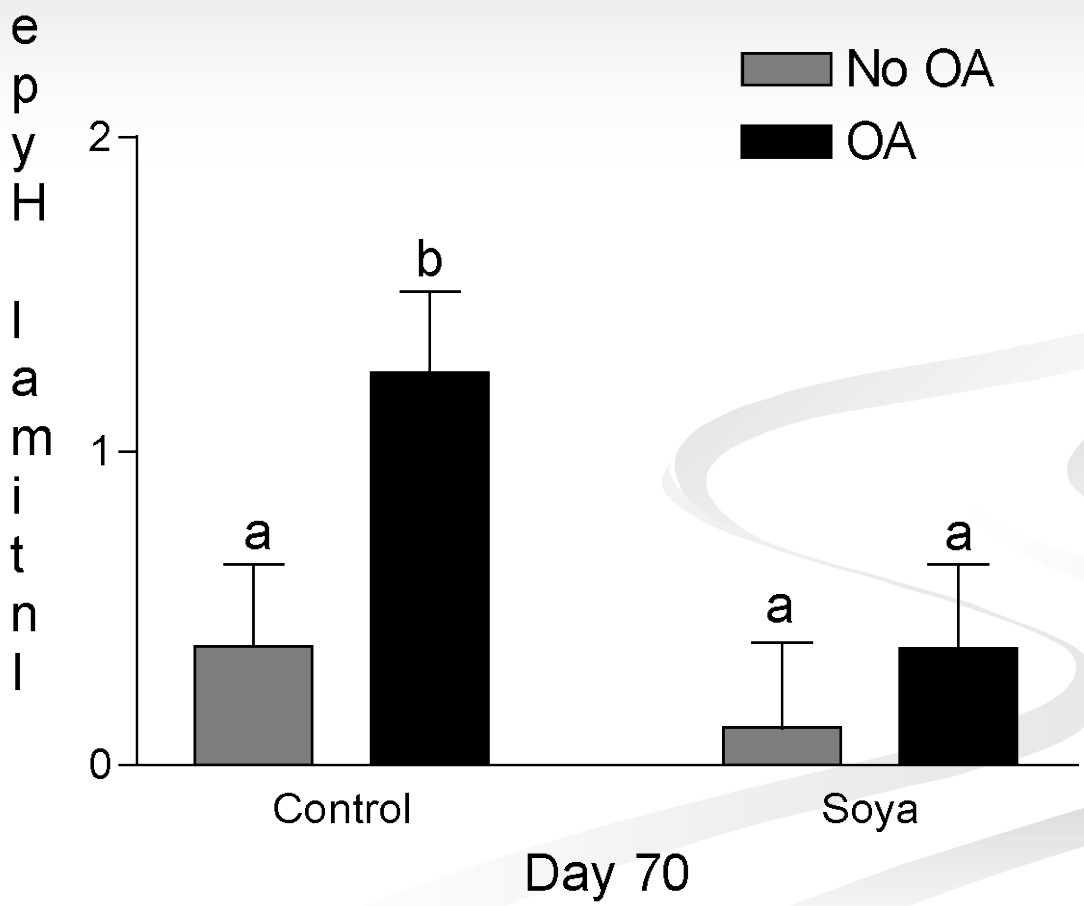
Intimal Hyperplasia



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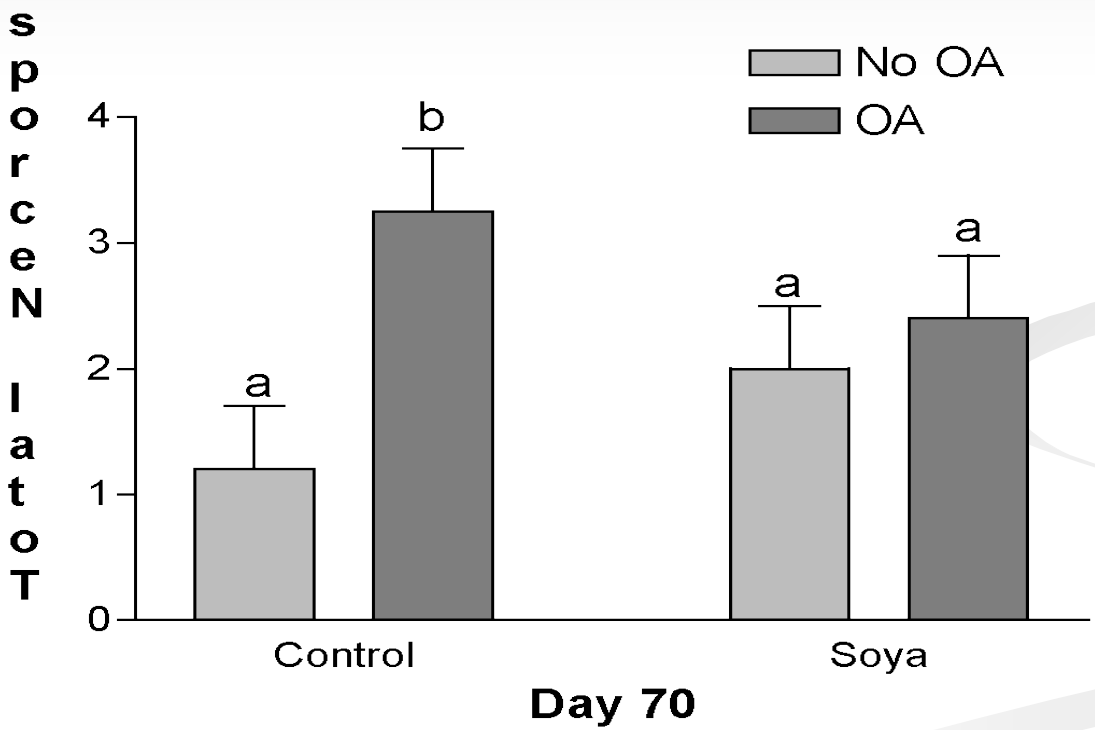
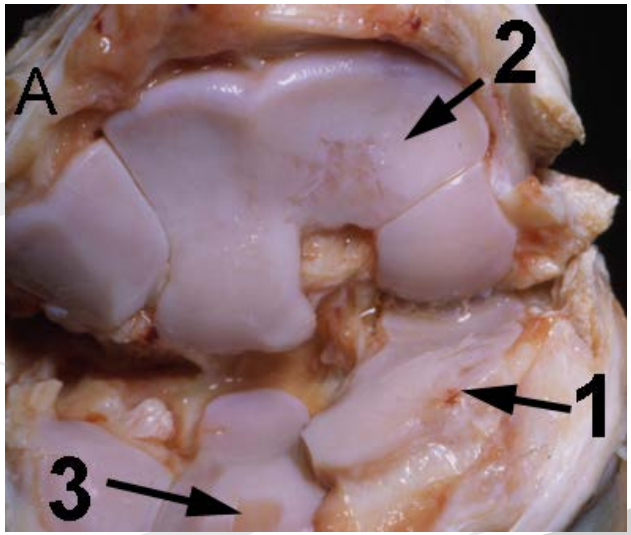
Cartilage disease score





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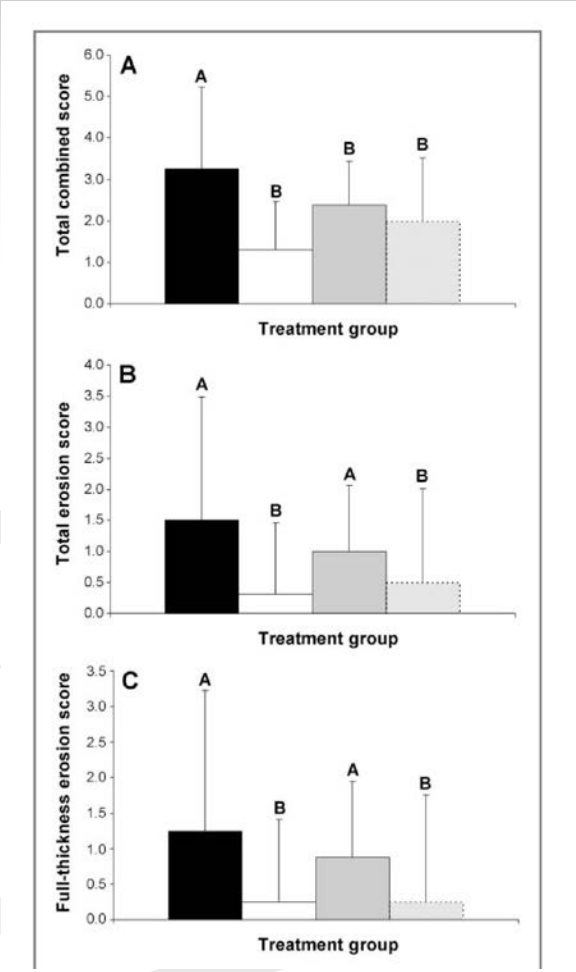
ASU in the Horse

- Significant reduction in severity of articular erosion & synovial hemorrhage compared to placebo-treated horses
- Significant increase in articular cartilage glycosaminoglycan synthesis compared to placebo treated horses



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Other companies have product with ASU (different than Vetoquinol product)

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Polyunsaturated Fatty Acids (PUFAs)

- Omega-3 (n-3) PUFAs contain α-linolenic acid that is desaturated in body to produce eicosapentaenoic acid & docosahexaenoic acid analogs of arachidonic acid
- Found in oily fish & fish oils
- Decrease production of inflammatory cytokines, prostaglandins, aggrecanases, thromboxanes, leukotrienes, reactive oxygen species

Aggrecanase is an important target in joint inflammation

- reIL-1βin carpal joints
- Expression of deleterious mediators
- ADAMTS-4 (aggrecanase-1) increased in synovial membrane
- ADAMTS-4 &-5 (aggrecanase-1&-2) increased in articular cartilage

0 (2012) 1583–1590

Evaluation of the inflammatory response in experimentally induced synovitis in the horse: a comparison of recombinant equine interleukin 1 beta and lipopolysaccharide

T.N. Ross †‡, J.D. Kisiday †, T. Hess ‡, C.W. McIlwraith †*

† Department of Clinical Sciences and Gail Holmes Equine Orthopaedic Research Center, Colorado State University, Fort Collins, CO 80523, USA
‡ Department of Animal Science, Colorado State University, Fort Collins, CO 80523, USA

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In vivo Study of PUFAs in Equine Joint Inflammation

- Lower expression of aggrecanase-1 in inflamed synovial membrane
- Modest decrease in activity of other mediators..real therapeutic value still to be proven

Journal of
Animal Physiology and Animal Nutrition

DOI: 10.1111/jpn.12359

ORIGINAL ARTICLE

Influence of an *n-3* long-chain polyunsaturated fatty acid-enriched diet on experimentally induced synovitis in horses

T. N. Ross-Jones[1], C. W. McIlwraith[2], J. D. Kisiday[2], T. M. Hess[1], D. K. Hansen[1] and J. Black[1,2]

1 Department of Animal Science, Colorado State University, Fort Collins, CO, USA, and
2 Gail Holmes Equine Orthopaedic Research Center, Department of Clinical Sciences, Colorado State University, Fort Collins, CO, USA

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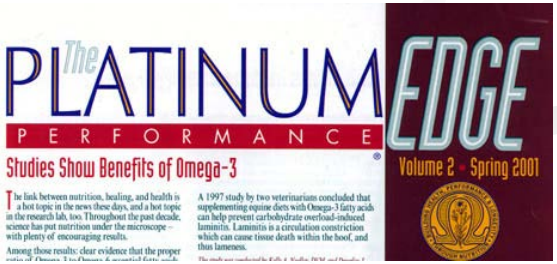
PUFAs have been incorporated into some OJSs

- Rare earth minerals
- Omega 3 fatty acids
- Scientific support for n-3 fatty acids
  - Inhibit aggrecanase
  - Inhibit COX2 & 5- lipooxygenase
  - Inhibit autocrine synthesis of IL-1 & TNF-α
- A different type of nutraceutical
- Getting studied in horse


The PLATINUM EDGE
PERFORMANCE
Studies Show Benefits of Omega-3
Volume 2 • Spring 2001

Osteoarthritis and Cartilage (2009) **17**, 896–905

doi:10.1016/j.joca.2008.12.009

Osteoarthritis and Cartilage | ICRS International Cartilage Repair Society | OARSI Osteoarthritis Research Society International

Relative efficacies of omega-3 polyunsaturated fatty acids in reducing expression of key proteins in a model system for studying osteoarthritis

Z. Zainal[a], A. J. Longman, S. Hurst, K. Duggan, B. Caterson, C. E. Hughes* and J. L. Harwood
School of Biosciences, Cardiff University, Cardiff CF10 3AX, UK

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Cetyl Myristoleate (CM)

- Another fatty acid..ester of myristoleic acid
- CM mat act by inhibition of 5-lipooxygenase pathway
- Product containing CM, GU, MSM & hydrolyzed collagen (Myristol™) evaluated in blind controlled study with 39 horses
- Myristol group improved significantly more than placebo group in AAEP lameness score, VAS, response to flexion, lameness after flexion

Effects of an Oral Nutraceutical on Clinical Aspects of Joint Disease in a Blinded, Controlled Clinical Trial: 39 Horses

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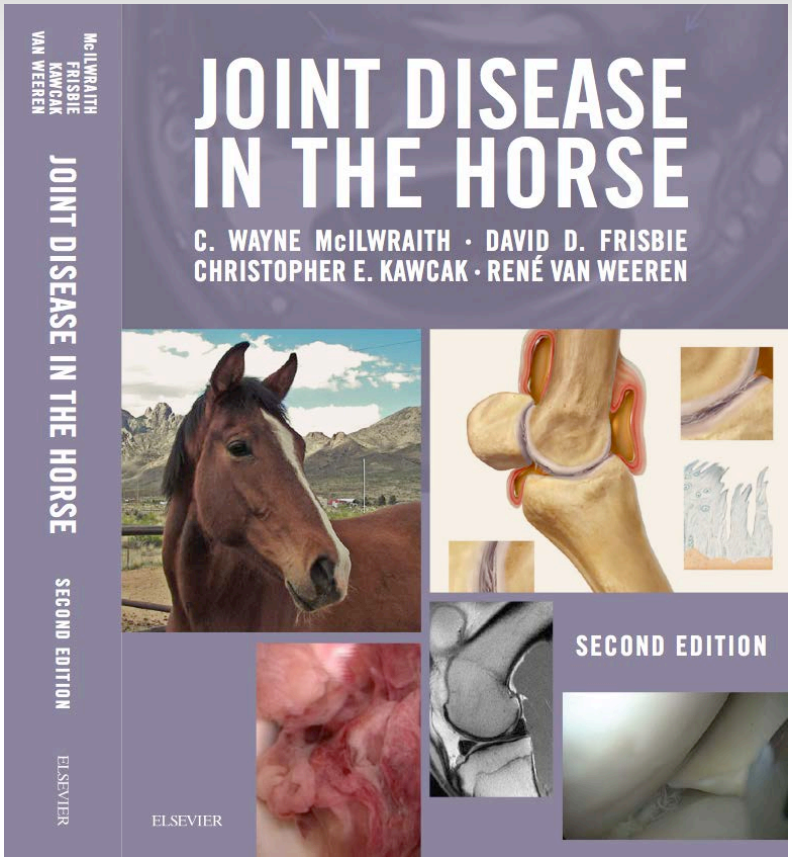
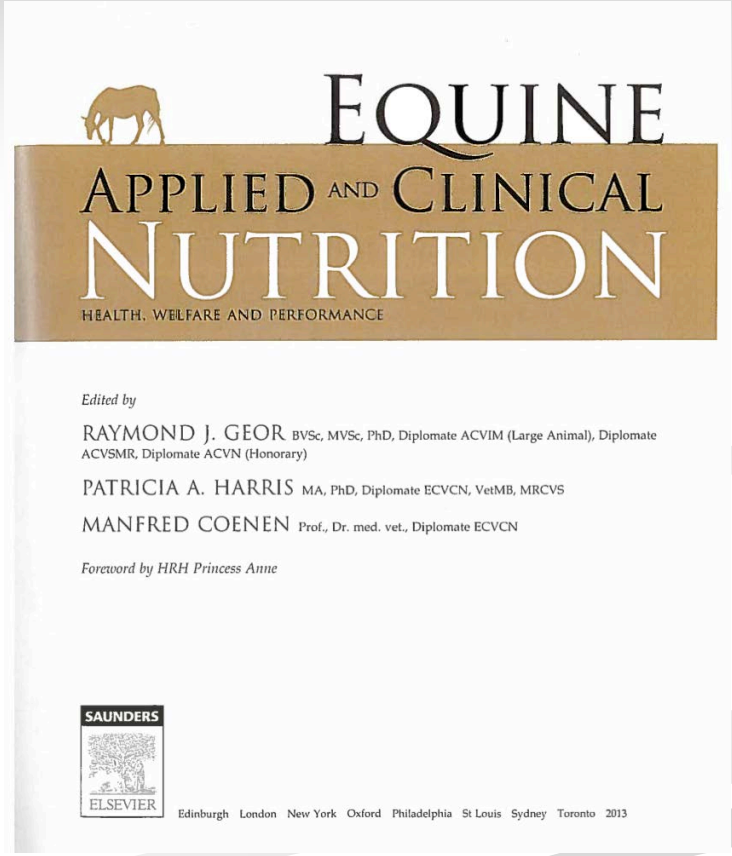
Can Supplements Strengthen Bone?

- Platinum Performance
  - Rare earth minerals that involved in bone metabolism
- OCD Pellets
  - Contain HA, silicon dioxide, amino acids, vitamins, micro-sized isolates
  - Silicon been shown to increase bone density

Further Reading





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