Viscosupplementation: The Magic of Hyaluronic Acid

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Primary Care Sports Medicine

Osteoarthritis of the knee

- Anatomic and mechanical problem
  - Wearing down of cartilage
- Biochemical problem
  - Changes in chondral and synovial homeostasis

Mechanical

- Chondral breakdown leads to:
  - Malalignment (unicompartmental – varus, valgus)
  - Increased subchondral stress
    - Sclerotic/cystic changes, bony edema
    - PAIN
  - Osteophyte formation
    - Loss of ROM and stiffness

Outerbridge (1961, patellar lesions)

- Grade 0: Normal articular cartilage
- Grade I: Softening and swelling of cartilage (chondromalacia)
- Grade II: Fragmentation/fissuring of surface, diameter less than $^{1}/_{2}$inch
- Grade III: Fragmentation/fissuring to subchondral bone, area greater than $^{1}/_{2}$inch
- Grade IV: Exposed subchondral bone

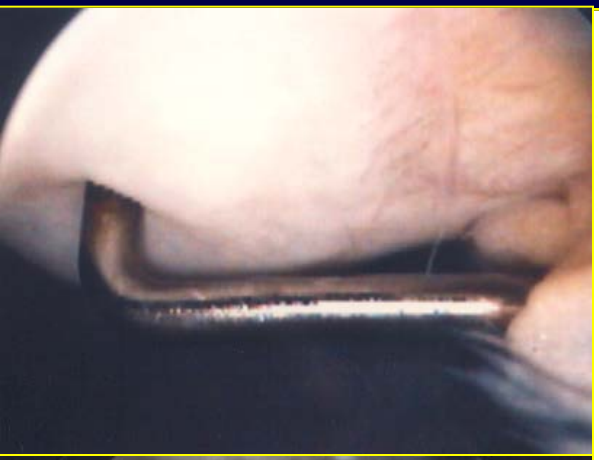
Insall Modification (1976, commonly used)

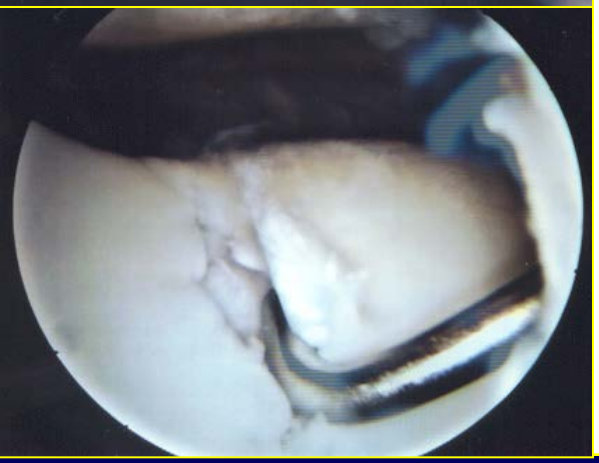
- Grade I: Softening and swelling of cartilage
- Grade II: Fibrillations
- Grade III: Deep fissures extending to subchondral bone
- Grade IV: Erosive changes with exposure of subchondral bone

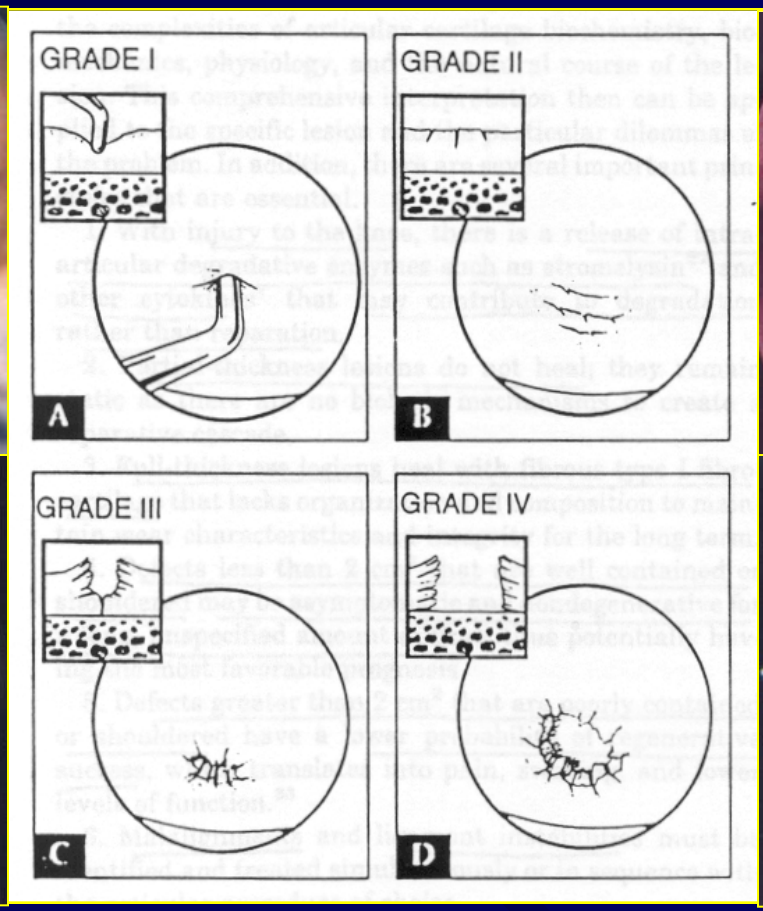
Noyes (1989)

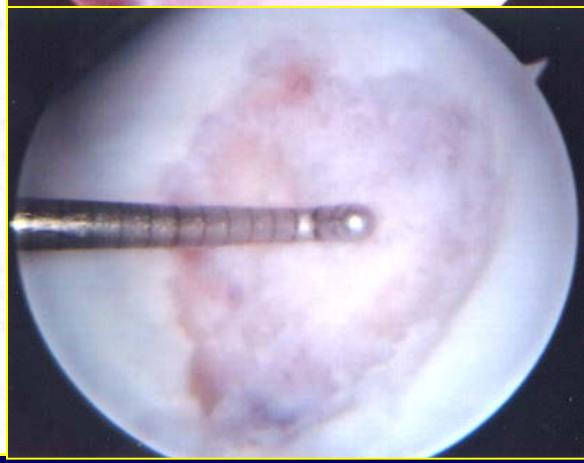
- Grade I: Chondromalacia
  - A) soft
  - B) softening with indentation
- Grade II: Open lesion
  - A) half thickness fissures/fragmentation
  - B) full thickness
- Grade III: Bone
  - A) bone exposed
  - B) bone cavity

ARTICULAR CARTILAGE
Outerbridge Classification









- Cartilage degeneration does not necessarily cause pain (articular cartilage has no pain receptors)
- Subchondral pain is a late event
- Synovial and capsular tissues are the primary sources of pain – not due to mechanical changes

"Knee pain is the malady–not osteoarthritis"
– Hadler

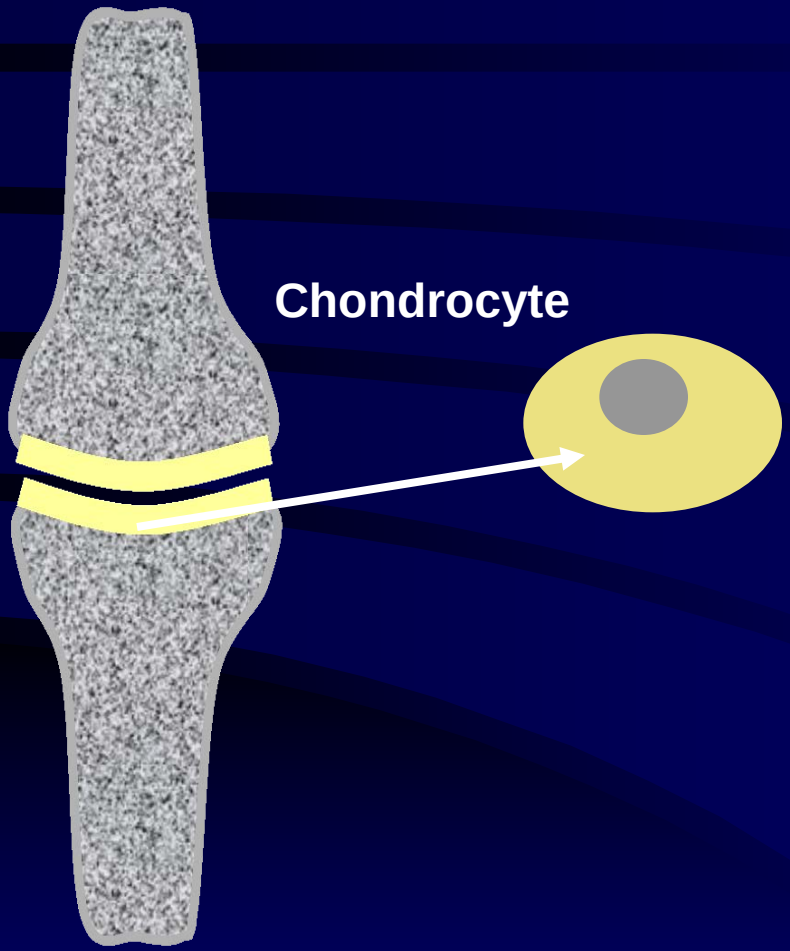
Pain drives osteoarthritis treatment

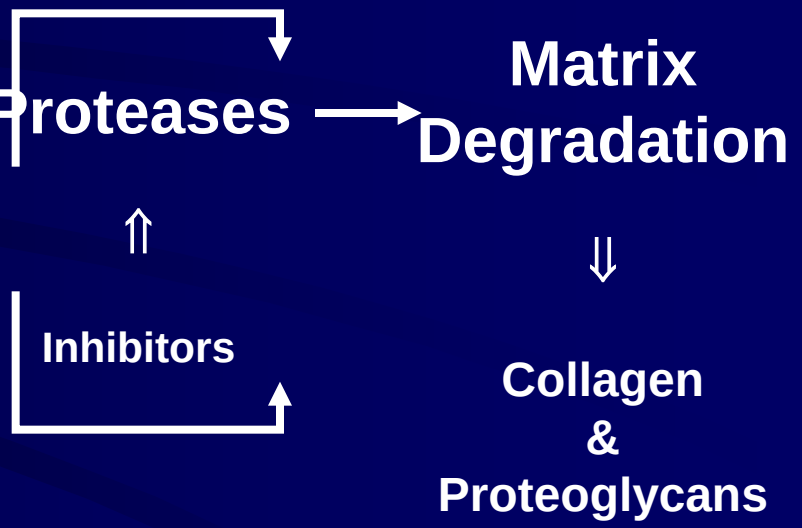
Reference: Hadler NM. Knee pain is the malady—not osteoarthritis. *Ann Int Med*. 1992;116(7):598-599.

Biochemical problem

- Chondrocyte and synovial changes in homeostasis
- Most important in understanding current and future treatments of OA

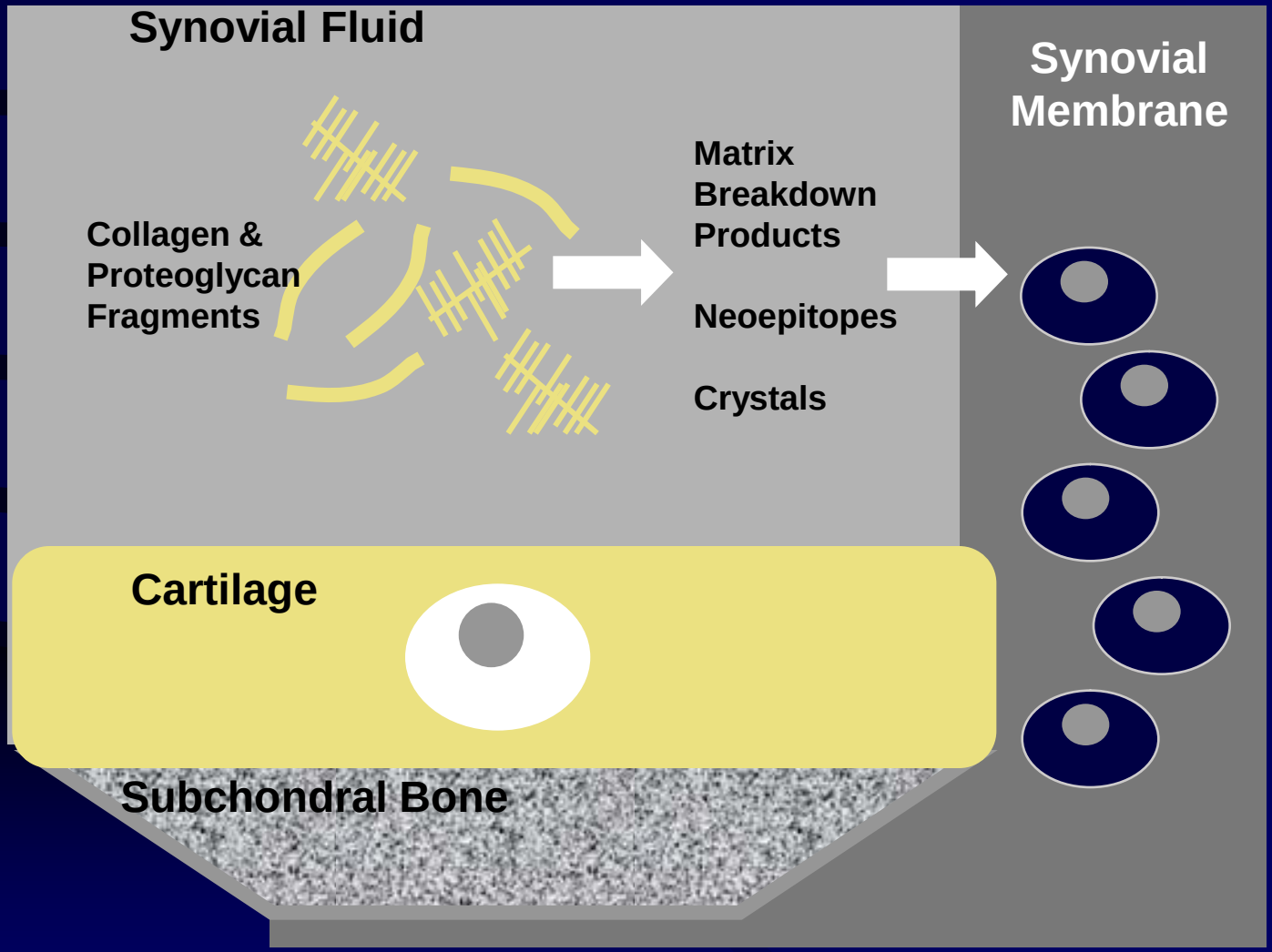
OA Disease Evolution – Stage I





Reference: Pelletier JP, Martel-Pelletier J, Howell DS. Etiopathogenesis of osteoarthritis. In: Koopman WJ, ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001;2:2195-2215.

OA Disease Evolution – Stage II



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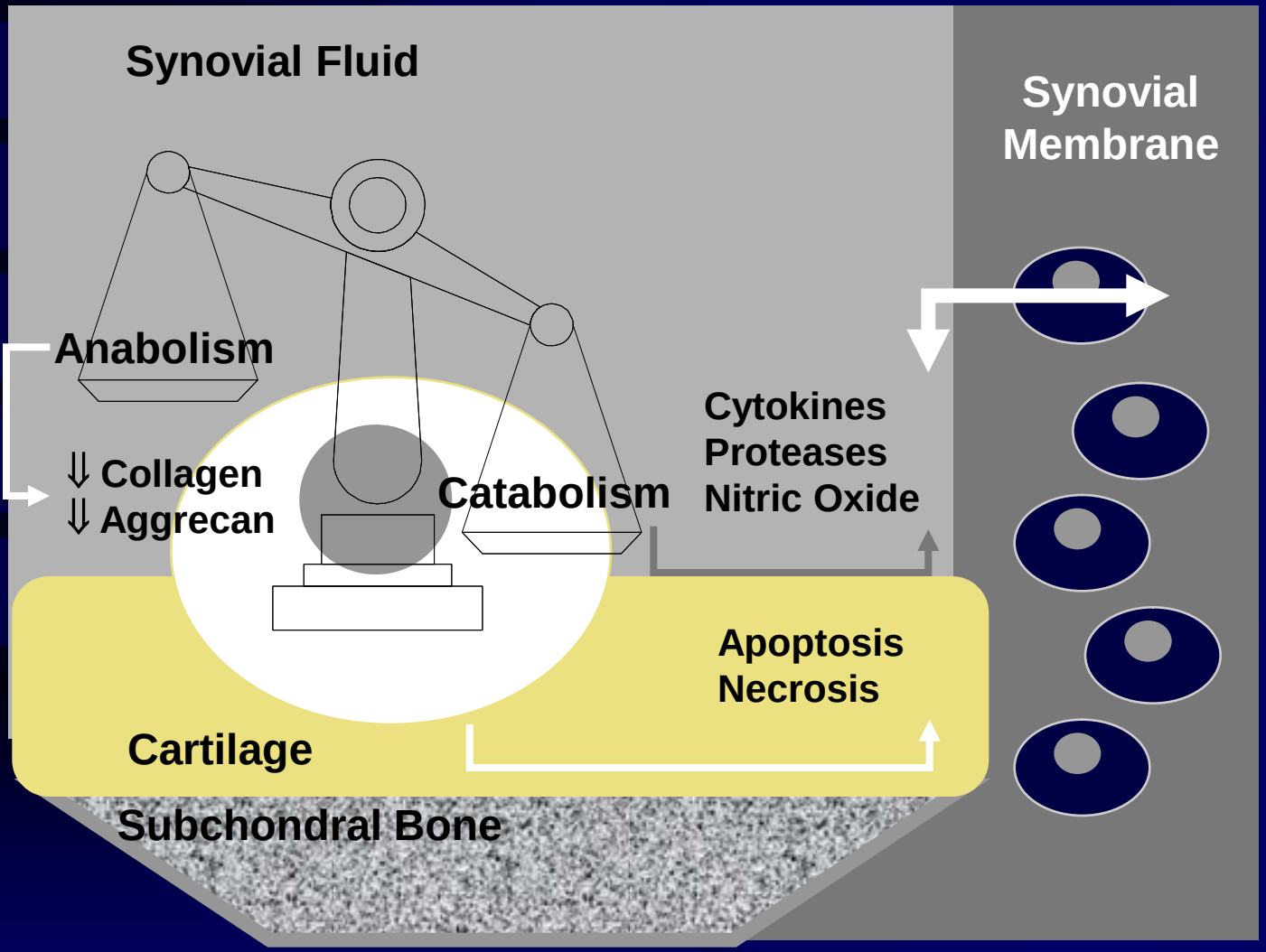
OA Disease Evolution – Stage III



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The Role of Inflammation in OA

- Inflammation secondary to cartilage degradation
- Morphological changes in OA synovium
  - Usually mild to moderate
  - At times comparable to rheumatoid arthritis
  - Characterized by increased numbers of:
    - Inflammatory mononuclear cells
    - Activated T-cells and B-cells

Reference: Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. *Arthritis Rheum*. 2001;44(6):1237-1247.

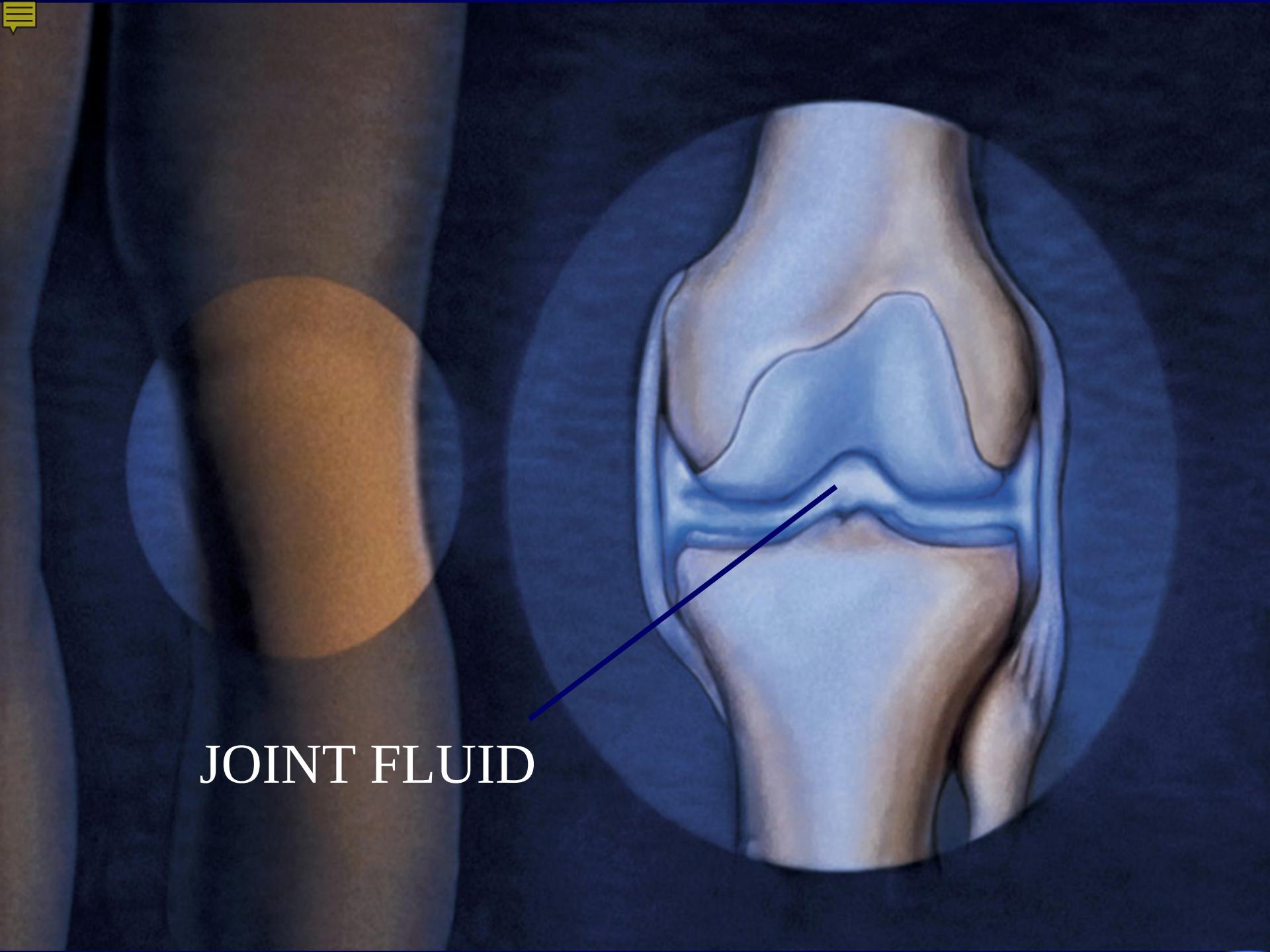
Functions of Hyaluronic Acid (HA) in the Normal Joint

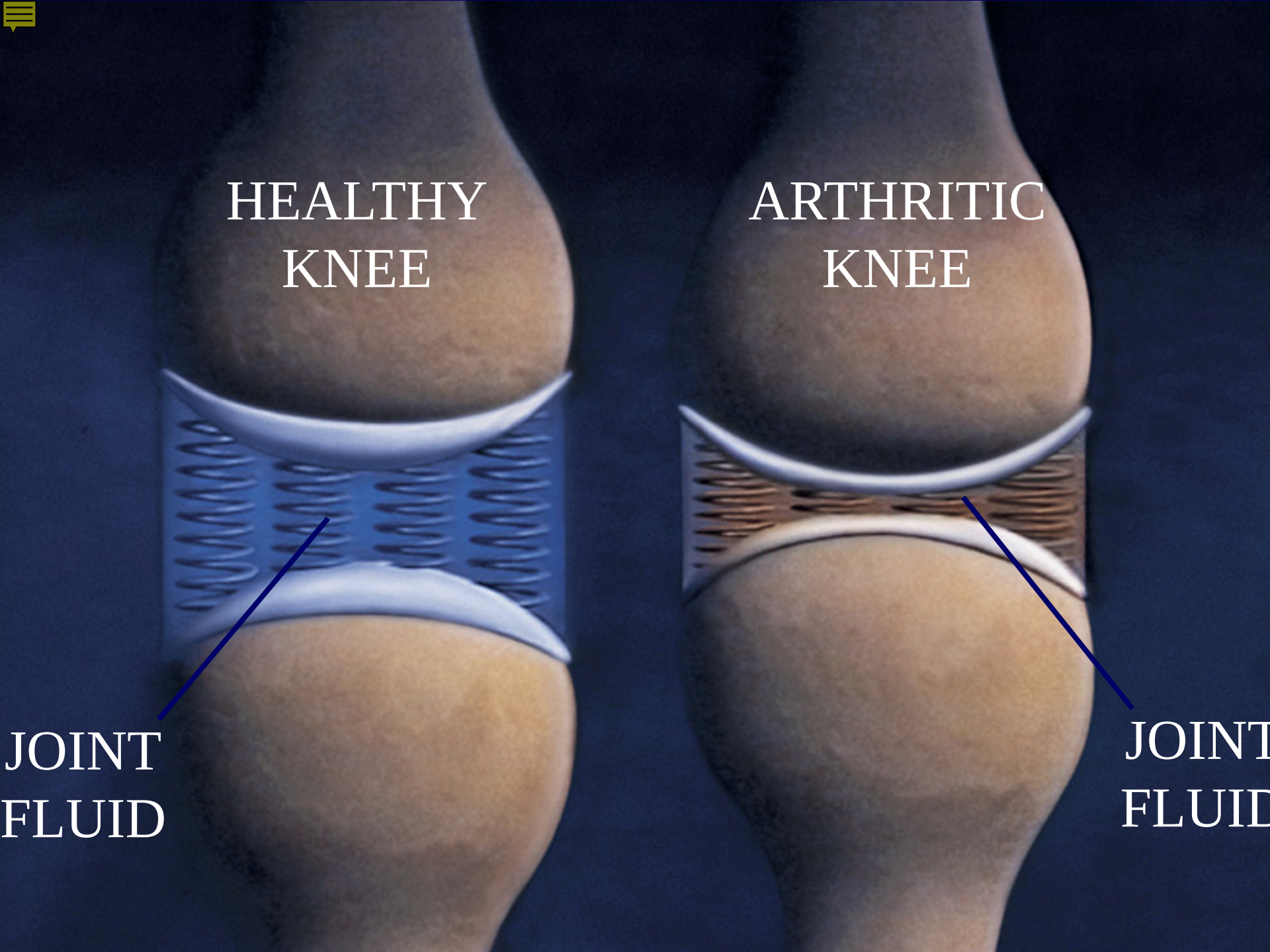
- Hyaluronic acid (HA) plays a key role in homeostasis of the normal joint
  - Macro-homeostasis – the rheological environment
  - Mini-homeostasis – the fluid environment
  - Micro-homeostasis – the chemical environment

Reference: Adams ME. Viscosupplementation as articular therapy. In: Laurent TC, ed. *The Chemistry, Biology, and Medical Applications of Hyaluronan and its Derivatives.* London, England: Portland Press, Ltd; 1998:243-253.

Macro-homeostasis: HA in Synovial Fluid (SF)

- Highly influences intercellular matrices of joint soft tissues
- Unique combination of elasticity and viscosity
- Hyaluronan responsible for elastoviscous properties
- Elastoviscosity critical for joint function


JOINT FLUID


HEALTHY
KNEE
ARTHRITIC
KNEE
JOINT
FLUID
JOINT
FLUID

Synovial Fluid Elastoviscosity

	Dynamic Moduli at 2.5 Hz	
	Elasticity (Pa)	**Viscosity** (Pa)
Normal (18- to 27-year-olds; n=16)	117 ± 13	45 ± 8
Osteoarthritic (n=11)	8 ± 5	5 ± 3

Reference: Balazs EA. The physical properties of synovial fluid and the special role of hyaluronic acid. In: Helfet AJ. *Disorders of the Knee*. 2nd ed. Philadelphia, Pa: JB Lippincott Company; 1983:61-74.

Molecular Weight, Elasticity, and Viscosity[1-7]

Comparison of Rheologic Factors			
	Molecular Weight (millions daltons)	Shock Absorption (elasticity Pa at 2.5 Hz)	Lubrication (viscosity Pa at 2.5 Hz)
Healthy, Young* Synovial Fluid [2,3] * In 18- to 27-year-olds	**4 - 5**	**117**	**45**
Osteoarthritic Synovial Fluid [3,4]	**0.5 - 4**	**8**	**5**
SYNVISC® (Hylan G-F 20) [1]	**6**	**111**	**25**
Hyalgan® (Sodium Hyaluronate) [5,6]	**0.6 - 0.7**	**0.6**	**3**
Supartz® (Sodium Hyaluronate) [5,7]	**0.6 - 1**	**9**	**16**

References: 1. SYNVISC® (Hylan G-F 20) Product Information. 2. Balazs EA, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol.* 1993;20(suppl 39):3-9. 3. Balazs EA, Denlinger JL. The role of hyaluronic acid in arthritis and its therapeutic use in: Peyron JG, ed. *Osteoarthritis: Current Clinical and Fundamental Problems*. France: Rueil-Malmaison, Laboratories Ciba Geigy; 1985:165-174. 4. Data on file, Genzyme Biosurgery. 5. Peyron JG. A new approach to the treatment of osteoarthritis: viscosupplementation. *Osteoarthritis Cartilage.* 1993;1:85-87. 6. Hyalgan® Product Information, Sanofi Pharmaceuticals, Inc. 7. Supartz® Product Information, Seikagaku Corporation.

Left: Supartz® (sodium hyaluronate)
MW 0.6-1

Center: SYNVISC® (Hylan G-F 20)
MW 6 million

Right: Hyalgan® (sodium hyaluronate)
MW 0.6-0.7

Supartz is a registered trademark of Seikagaku Corporation.
Hyalgan is a registered trademark of FIDIA S.p.A.

Hylans and hyaluronan

- Cross-linked hyaluronan
- Increased molecular weight (hylan A) or continuous molecular network (hylan B)
- Higher elastoviscosity than purified hyaluronan
- Longer tissue residence time

SYNVISC® (Hylan G-F 20)

- Elastoviscosity similar to that of the synovial fluid of healthy 18- to 27-year-olds
- Designed as a synovial fluid prosthetic device
- A series of three injections can provide pain relief for months
- Generally well tolerated in trials and clinical practice

Reference: Weiss C, Band P. Basic principles underlying the development of viscosupplementation for the treatment of osteoarthritis. *J Clin Rheumatol.* 1999;5:S2-S11.

Molecular weight, viscosity and elasticity are not the only factors . . . .

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MW 6 million

Right: Hyalgan® (sodium hyaluronate)
MW 0.6-0.7

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HA Mini-Homeostasis

- Intrinsic autoregulatory function
  - Regulates lymphatic flow
  - Regulates diffusion of nutrients
  - Regulates diffusion of waste products

Reference: Adams ME. Viscosupplementation as articular therapy. In: Laurent TC, ed. *The Chemistry, Biology, and Medical Applications of Hyaluronan and its Derivatives.* London, England: Portland Press, Ltd; 1998:243-253.

HA Micro-Homeostasis

- Effective free-radical scavenger
- Protects chondrocytes and synoviocytes from degradative enzymes, chemical agents, and toxins
- Stabilizes cell membranes
- Desensitizes sensory receptors
- Auto-regulatory maintaining environment for normal HA synthesis

Reference: Adams ME. Viscosupplementation as articular therapy. In: Laurent TC, ed. *The Chemistry, Biology, and Medical Applications of Hyaluronan and its Derivatives.* London, England: Portland Press, Ltd; 1998:243-253.

Viscosupplementation

- Replaces pathologic synovial fluid
- Supplements elasticity and viscosity
- Reduces pain, improves mobility and protects cartilage

Indications for Viscosupplementation

Indicated for the treatment of pain in osteoarthritis of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics, e.g., acetaminophen

SYNVISC® Plus Appropriate Care (AC) vs. AC Alone[1,2]

- 3 injections, 1 week apart of SYNVISC® plus AC vs. AC alone
- Prospective
- Randomized
- Multicenter
- Pragmatic

References: 1. Raynauld J-P, Torrance GW, Band PA, et al. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (part 1 of 2): clinical results. *Osteoarthritis Cartilage.* 2002;10:506-517. 2. Data on file, Wyeth Pharmaceuticals.

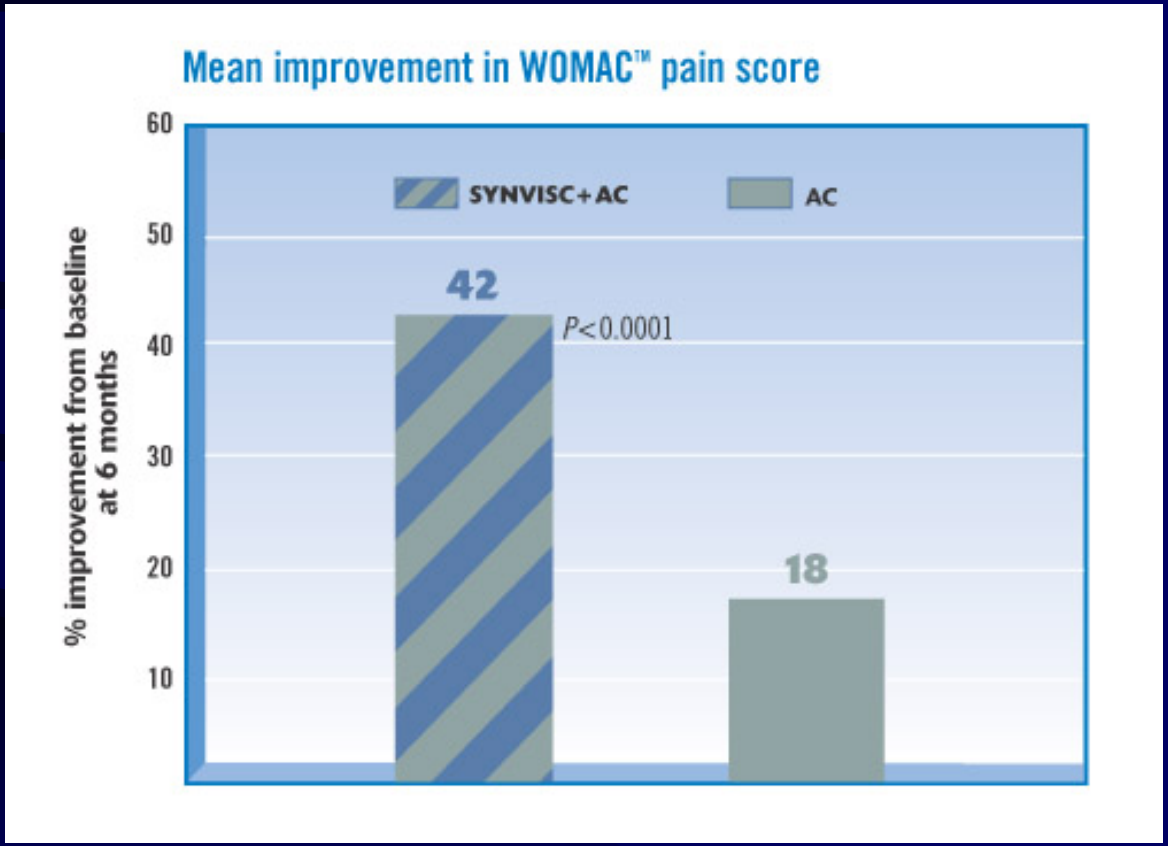
Appropriate Care

Physicians were free to establish appropriate care; they were encouraged, however, to use the 1995 American College of Rheumatology Treatment Guidelines for OA of the knee.[1] "Appropriate care" could include any combination of

- Analgesics
- NSAIDs
- Corticosteroid injections
- Education and counseling
- Weight loss
- Joint rest
- Heat or ice
- Assistive devices
- Physical therapy
- Arthroscopy
- Total joint replacement

Reference: 1. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. *Arthritis Rheum.* 1995;38:1541-1546.

SYNVISC® Plus Appropriate Care (AC) Was More Effective Than AC Alone at 6 Months[1,2]



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Viscosupplementation vs. corticosteroid injection (cortisone shot)

Physicians' Perceptions: Pro-corticosteroids

- Familiarity — long established in the treatment paradigm.[1]
- Used to reduce pain and inflammation, especially in acute knee OA flare-ups[1]
- Relatively fast-acting[1]
- Familiarity with injection procedure
  - Needle placement accuracy is felt to be less critical than for viscosupplementation; being near the target can result in reasonable efficacy

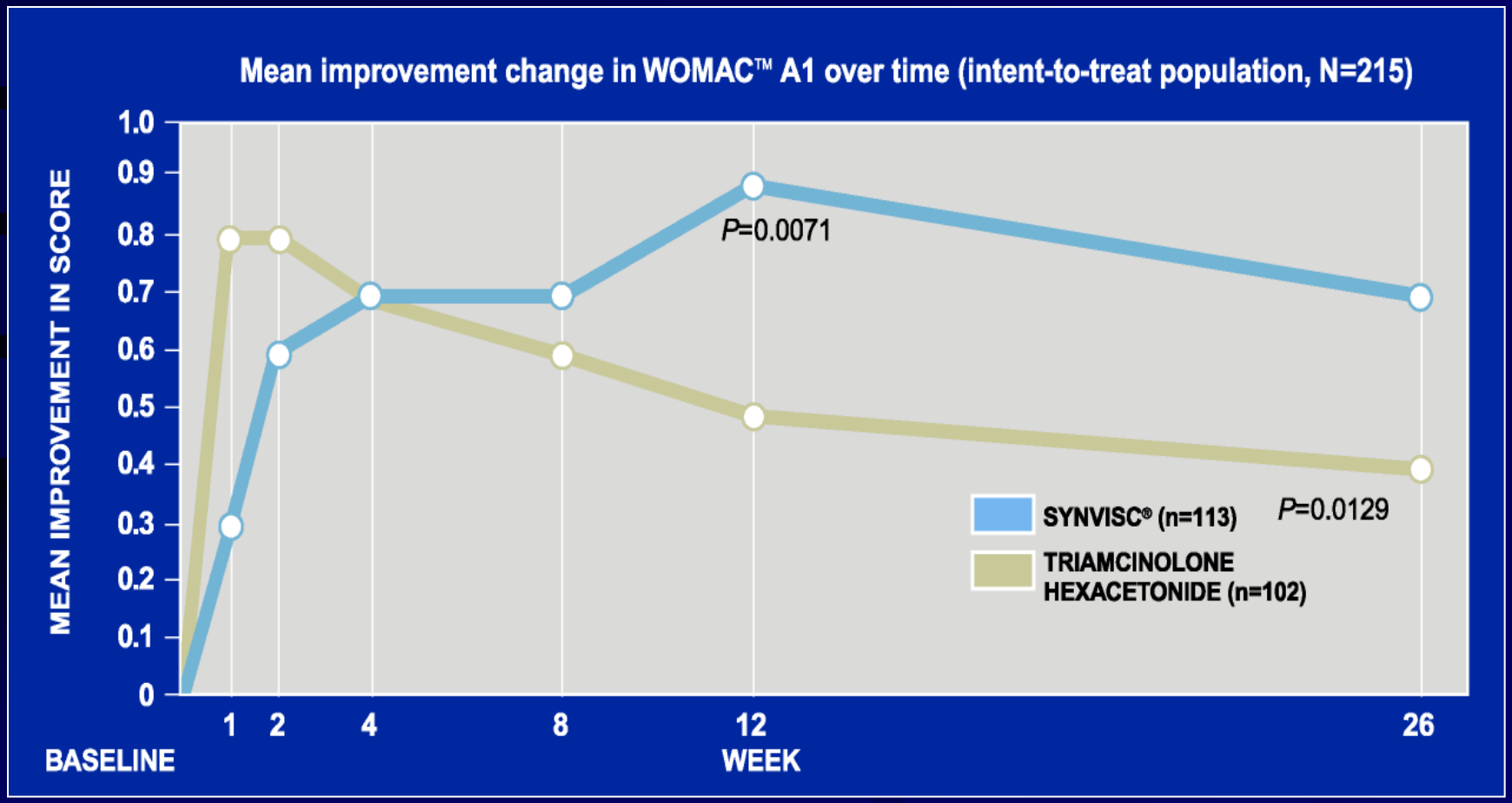
Physicians' Perceptions: Anti-corticosteroids

- Short duration of efficacy[1]
- Can require frequent injections[2,3]
- Frequent injections (>3 per year) may cause cartilage damage[2,3]
- Local adverse effects
  - Post-injection flares[4]
  - Skin atrophy[5]
  - Osteonecrosis[5]

Viscosupplementation vs. an Intra-articular Corticosteroid

- SYNVISC®: three 2-mL intra-articular injections, 1 week apart
- Triamcinolone hexacetonide: 1 injection as 2 mL of a 20-mg/mL suspension (40 mg)
- U.S.-based
- Multicenter, Prospective
- Physician observer-blinded
- 26 weeks
- **Reference:** Data on file, Wyeth Pharmaceuticals.

SYNVISC® (Hylan G-F 20) vs. an Intra-articular Corticosteroid

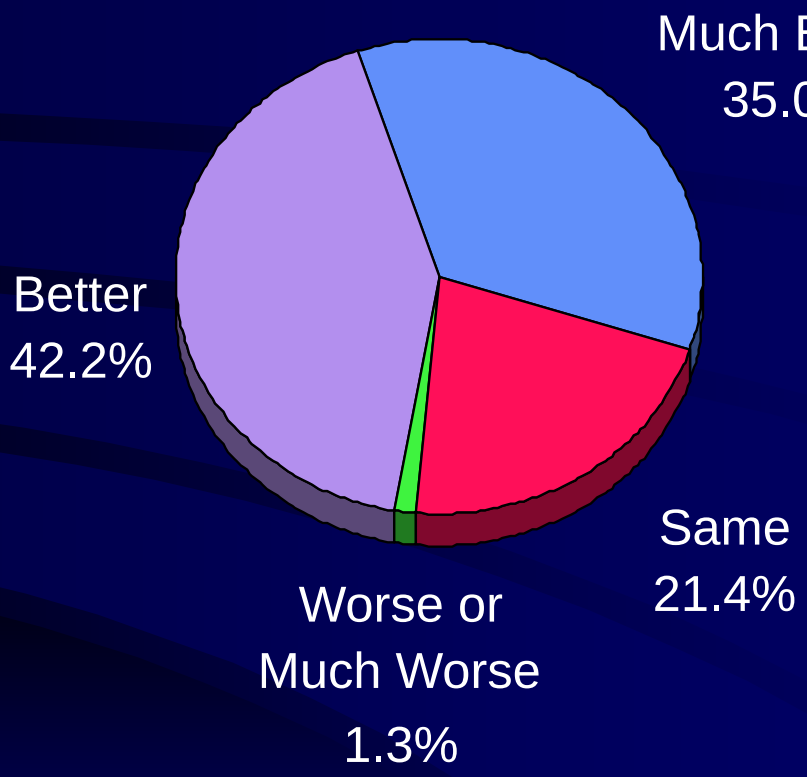


Reference: Data on file, Wyeth Pharmaceuticals.

What to expect with viscosupplementation?

- What are the chances I will get better?
- How is it given?
- How many times and how often?

Overall Response to Viscosupplementation



Reference: Lussier A, Cividino AA, McFarlane CA, et al. Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. *J Rheumatol*. 1996;23(9):1579-1585.

Severity of OA of the Knee: Grade 1 (Mild)

Severity of OA of the Knee: Grade 2 (Mild to moderate)

Severity of OA of the Knee: Grade 3 (Moderate to Severe)

Severity of OA of the Knee: Grade 4 (Severe)

Viscosupplementation Across All Radiologic Grades

Medial x-ray Grade	Percent Better or Much Better
I	91
II	80
III	76
IV	58

Reference: Lussier A, Cividino AA, McFarlane CA, et al. Viscosupplementation with hylan for the treatment of osteoarthritis: findings from clinical practice in Canada. *J Rheumatol*. 1996;23(9):1579-1585.

Dosing and Administering SYNVISC® (Hylan G-F 20)

- Prepare knee for injection
- Aspirate joint fluid
- Implant SYNVISC®

Reference: SYNVISC® (Hylan G-F 20) Product Information, Genzyme Biosurgery.

Dosing and Administering SYNVISC® (Hylan G-F 20)

- Course of therapy: 3 intra-articular injections over 15 days
  - Day 1: 2 mL
  - Day 8: 2 mL
  - Day 15: 2 mL

Reference: SYNVISC® (Hylan G-F 20) Product Information, Genzyme Biosurgery.

Dosing and Administering Hyalgan® and Supartz®

- Course of therapy: 5 intra-articular injections over 28 days

	Hyalgan	Supartz
• Day 1:	2 mL	2.5 ml
• Day 8:	2 mL	2.5 ml
• Day 15:	2 mL	2.5 ml
• Day 21:	2 mL	2.5 ml
• Day 28:	2 mL	2.5 ml

Precautions and Contraindications

- Side effects other than local pain/swelling reported rarely
- Contraindicated in patients with known hypersensitivity to hyaluronan products
- Use caution in patients allergic to avian proteins, feathers, or egg products; who have evidence of venous or lymphatic stasis in the leg to be treated; or who have severe inflammation in the knee joint to be treated

When do I use viscosupplementation?

- Stepwise approach to symptomatic OA
  - **First:** NSAIDs, braces/orthotics, glucosamine, PT, analgesics, activity modification, etc.
    - Why? - Knee hygiene
  - **Second:** Injections
    - Visco +/- preceded by steroid injection
    - Visco +/- aspirations

When I use Viscosupplementation beyond simple OA

- Osteoarthritis and meniscal tears
- Chondral defects / Contusions
- Chondromalacia / early OA in the athlete

Arthritis and meniscal tears

- Case study #1:
  - 65 yr old overweight female
  - Pain (predominantly anterior), swelling, stiffness
  - Tenderness over medial and lateral facets
  - Mild tenderness over medial joint line
  - No mechanical symptoms
  - ? Other medical problems
  - Imaging:
    - Patellofemoral OA (grade 3-4)
    - Medial meniscal tear, non-displaced

- Option #1 - Arthroscopy? Debridement/resection
  - Medial tenderness improved, still have anterior knee pain, stiffness and swelling
  - “Thanks for nothing doc”
- Option #2 - Viscosupplementation first
  - Anterior knee pain and stiffness 95% resolved – “Great, thanks doc”
  - Medial knee tenderness and occasional swelling persists on/off
  - Will be back another day if meniscal symptoms develop/worsen

Arthritis and meniscal tears

- Case study #2:
  - 65 yr old overweight female
  - Pain (predominantly medial), swelling, stiffness
  - Tenderness over medial joint line
  - No mechanical symptoms
  - ? Other medical problems
  - Imaging:
    - Medial compartment OA (grade 2-3, small area of grade 4)
    - Medial meniscal grade III degenerative changes

- Option #1 – Arthroscopy: 50% partial menisectomy
  - Swelling and stiffness slightly improved
  - Medial pain persists, slightly worse
    - “Thanks for nothing doc”
    - Why? Grade 3-4 chondral damage no longer protected by meniscus – increased subchondral stress
- Option #2 – viscosupplementation + (lateral heel wedge or unloader brace) first
  - Swelling and stiffness slightly improved
  - Medial pain 75% improved
  - When becomes unlivable – arthroscopy vs. unicompartmental replacement

Chondral defects

Outerbridge (1961, patellar lesions)

- Grade II: Fragmentation/fissuring of surface, diameter less than $^{1}/_{2}$inch
- Grade III: Fragmentation/fissuring to subchondral bone, area greater than $^{1}/_{2}$inch
- Grade IV: Exposed subchondral bone

Insall Modification (1976, commonly used)

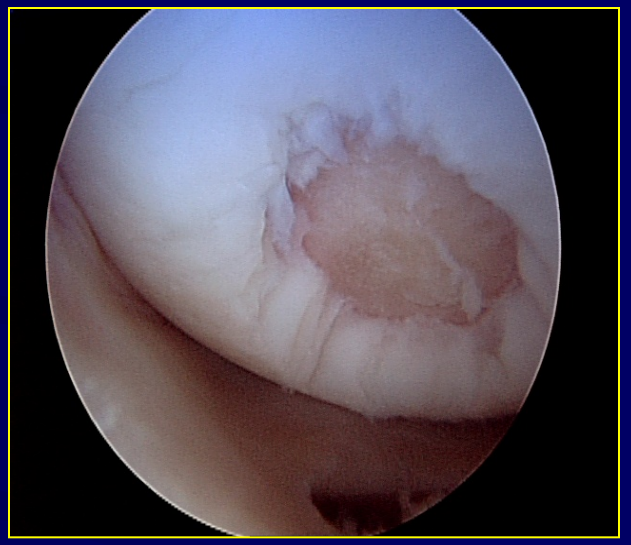
- Grade II: Fibrillations
- Grade III: Deep fissures extending to subchondral bone
- Grade IV: Erosive changes with exposure of subchondral bone

Noyes (1989)

- Grade II: Open lesion
  - A) half thickness fissures/fragmentation
  - B) full thickness
- Grade III: Bone
  - A) bone exposed
  - B) bone cavity

Articular Cartilage Injury vs. Osteoarthritis

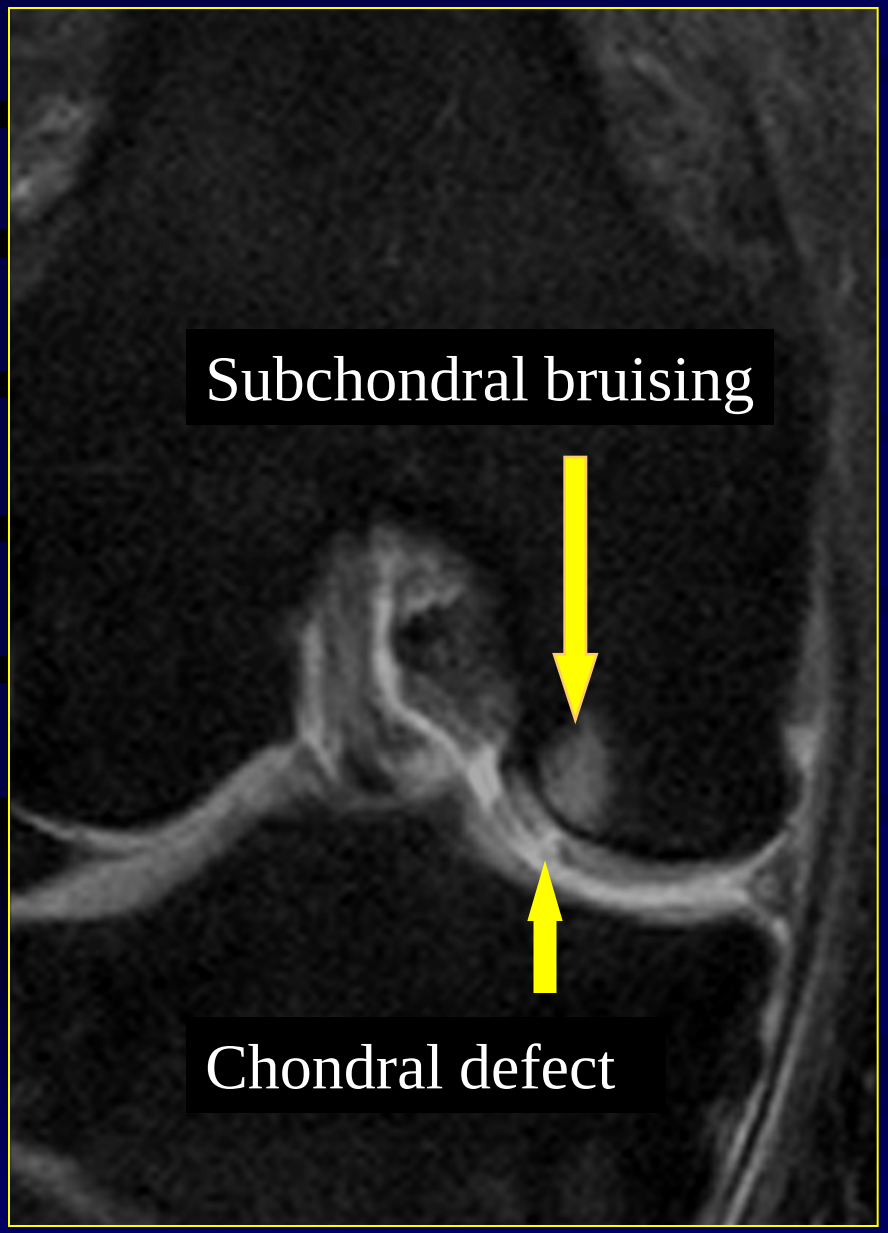
- Articular cartilage injury
  - acute, localized
  - acute, generalized
  - chronic, localized
  - chronic, generalized

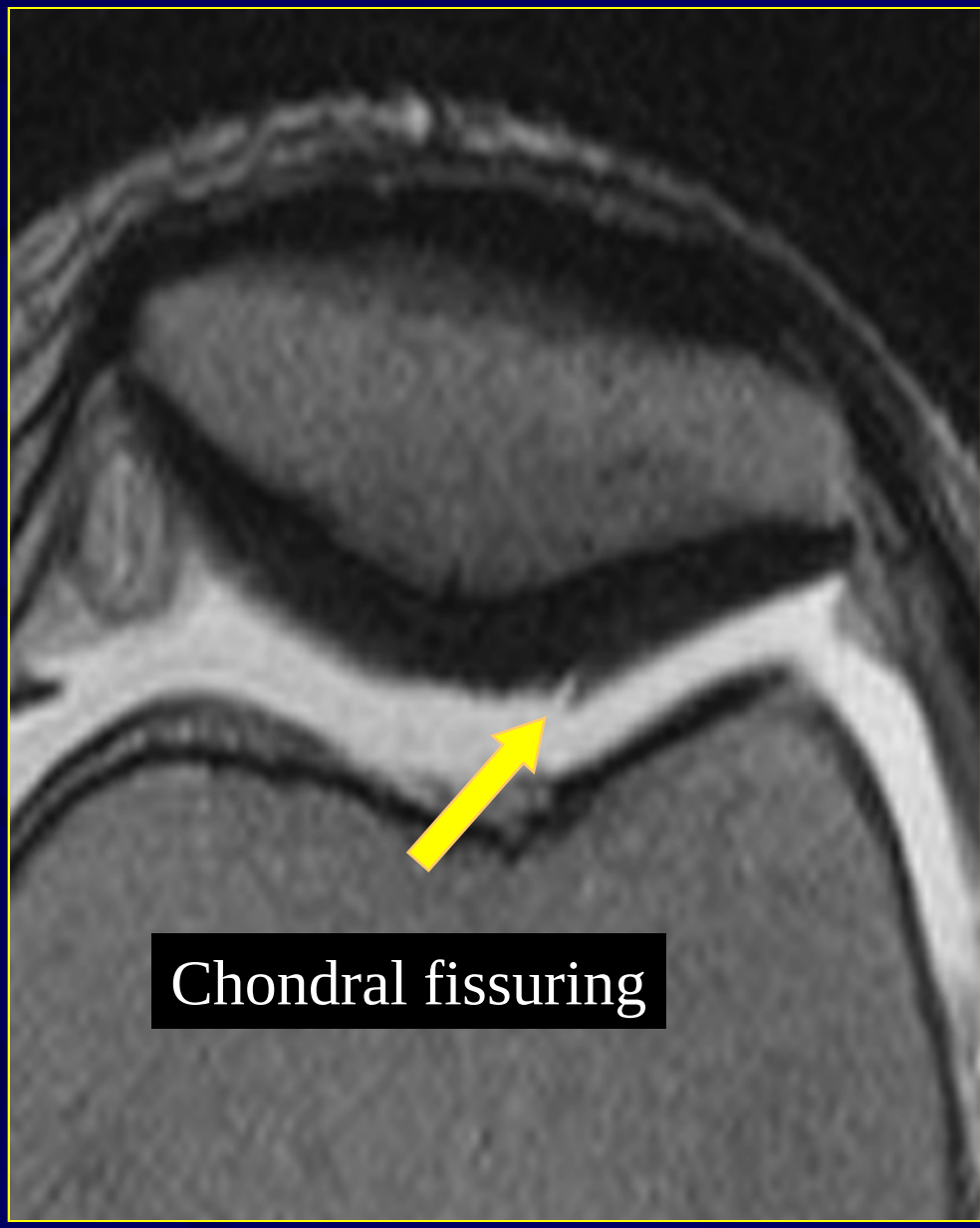


- Osteoarthritis
  - chronic, more generalized
  - radiographic changes

Generalized cartilage injury - arthritis

Localized cartilage injury – chondral defect

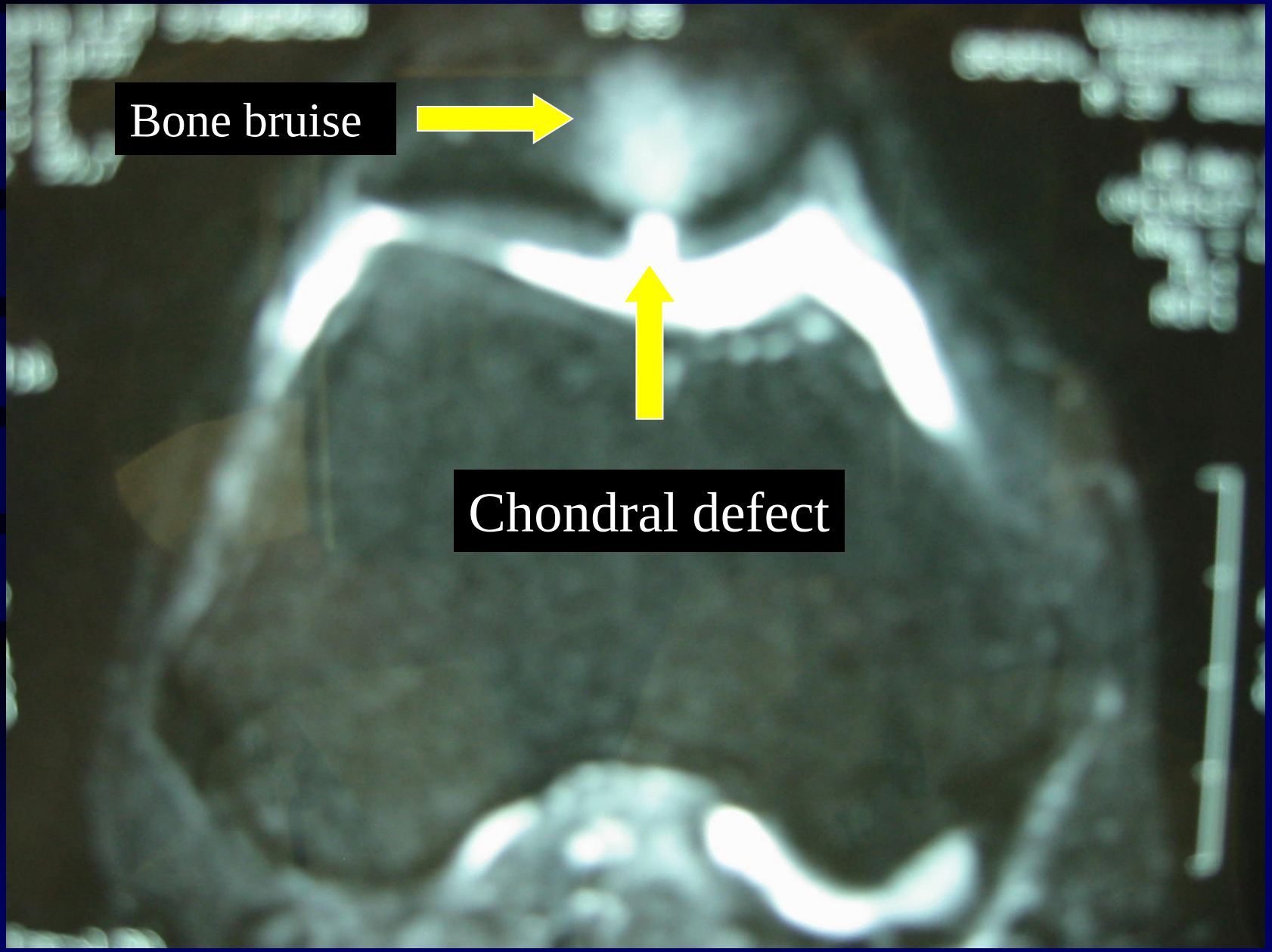

Subchondral bruising
Chondral defect


Chondral fissuring

Knee contusion may lead to cartilage surface contact and cartilage injury

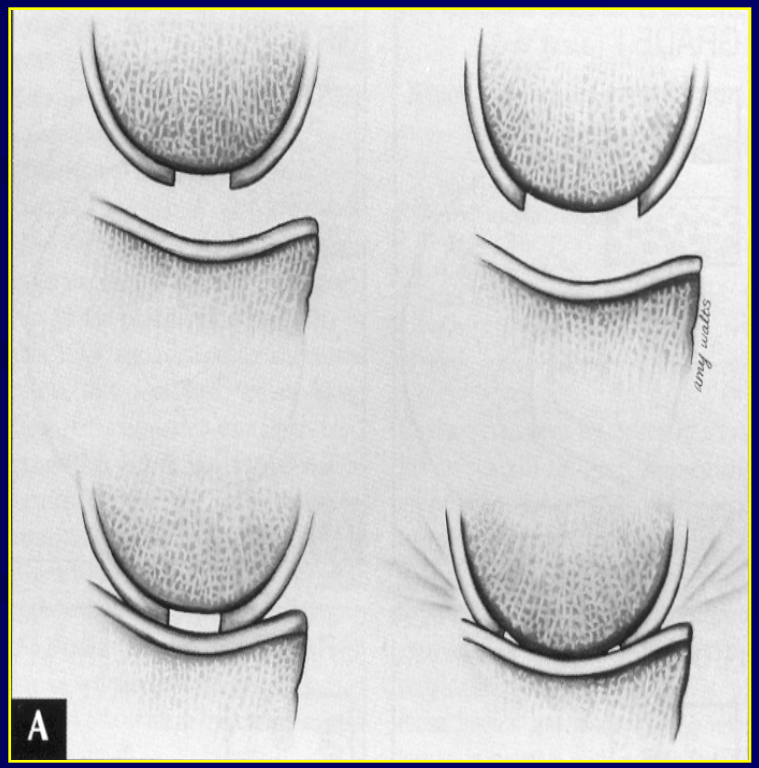
»Cartilage injury

- Chondral contusion vs chondral defect
  - Chondral contusion = cartilage bruise
    - Typically resolves with non-operative treatment
  - Chondral defect = cartilage “pot-hole”
    - May not resolve with non-operative treatment
    - Surgical referral?


Bone bruise
Chondral defect

Chondral Pathology

- The larger the lesion the less protective effect on the adjoining cartilage, subchondral bone, and “kissing surface”



Chondral defects

- Cartilage breakdown products
- Synovial inflammation
- Localized loss of mechanical viscoelastic properties
  - potential later generalized loss of viscoelastic properties as synovial fluid composition changes
- Many chondral defects are not amenable to chondroplasty, microfracture, ACI, etc
  - but all are amenable to viscosupplementation

Chondromalacia patella (cartilage injury)

- Chondromalacia:
  - Softening of the articular cartilage
  - A degenerative process
  - A pathologic diagnosis
  - May be idiopathic, but usually secondary to malalignment or instability

  - Sensitive cartilage

Chondromalacia and arthritis

Outerbridge (1961, patellar lesions)

- Grade I: Softening and swelling of cartilage (chondromalacia)

Insall Modification (1976, commonly used)

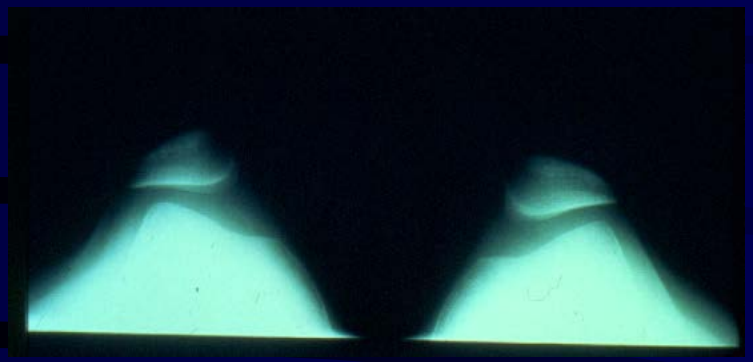
- Grade I: Softening and swelling of cartilage

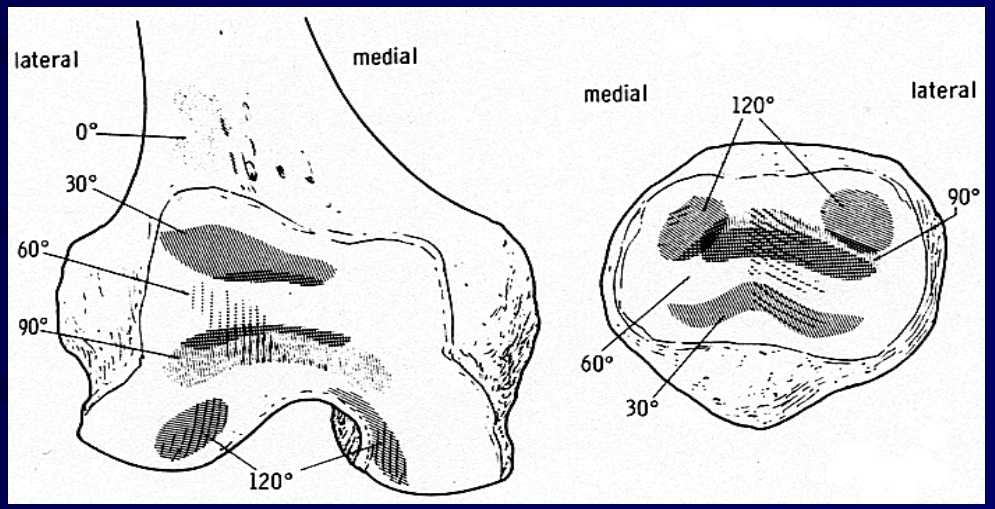
Noyes (1989)

- Grade I: Chondromalacia
  - A) soft
  - B) softening with indentation

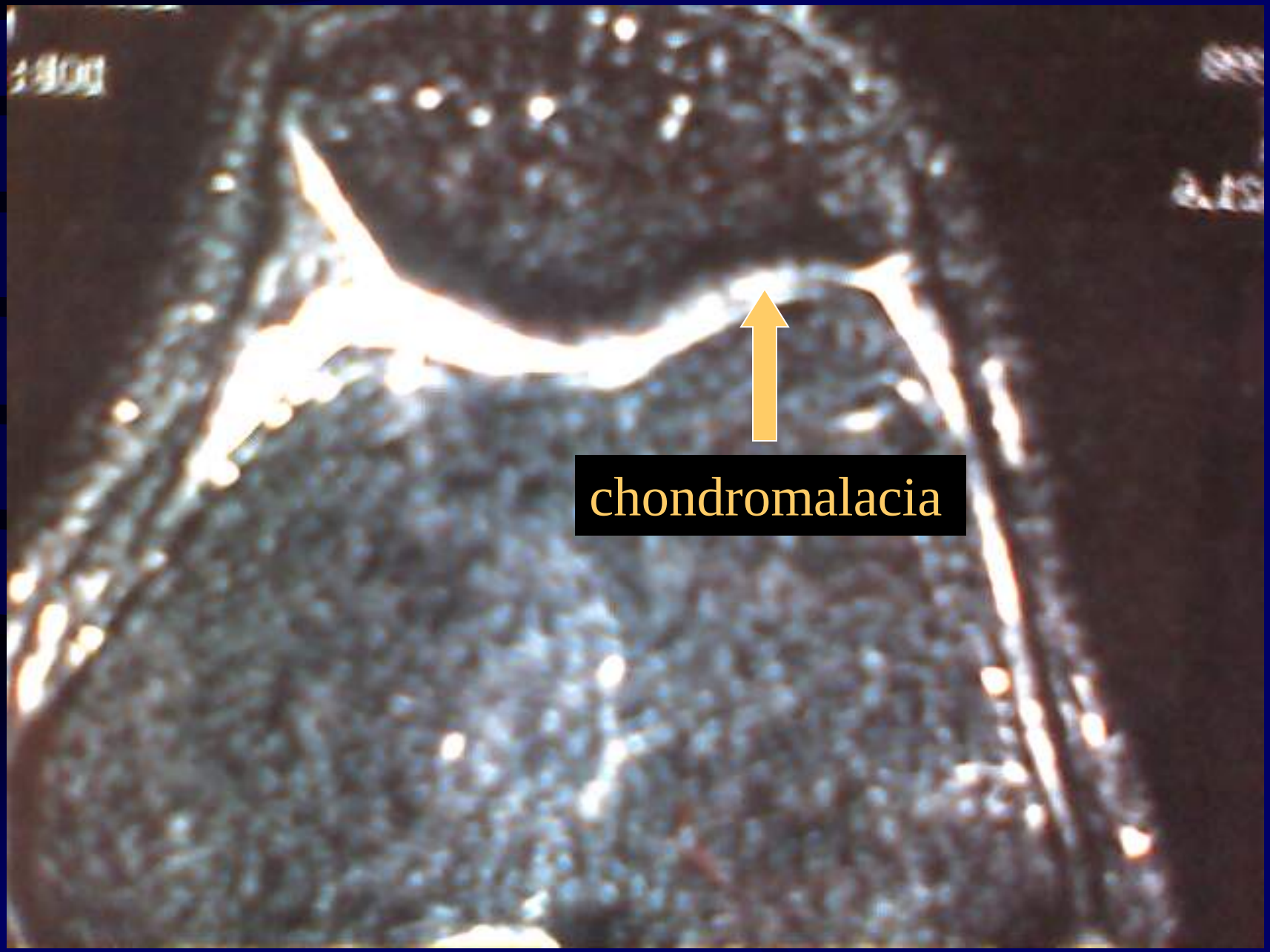
Cartilage Biomechanics

Patello-femoral contact patterns:





Femoral – tibial contact:


chondromalacia

Chondromalacia patella

- What do we do with this beyond NSAID's, PT, braces, activity modification, etc ?
- There is no surgery for chondromalacia
  - ? lateral release
- Will this progress to more advanced arthritis?

Viscosupplementation for the athlete (laborer/policeman/fireman/etc.)

- Pain with sport or activity only
- Viscosupplementation eliminates or minimizes symptoms to allow participation in sport/activity
- Does viscosupplementation alter the course of arthritis?
  - Decrease risk by increasing viscoelasticity and minimizing impact?
  - Increase risk by allowing increased participation in impact sports/activities?
- Maybe answers after future studies
- For now, athletes/workers make their own fully informed risk/benefit decisions

Viscosupplementation: Other applications/indications

- Hip, ankle, shoulder OA future indications
  - ?under flouroscopy
- Chondromalacia future indication
- Chronic painful shoulder future indication
  - tendinopathies

Viscosupplementation: summary

- Series of injections once per week for 3 or 5 weeks
- Can provide pain relief lasting months to years
- Series can be repeated in six months if pain returns

Thanks!