Non-operative Treatments for Osteoarthritis

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Three O's of Aging

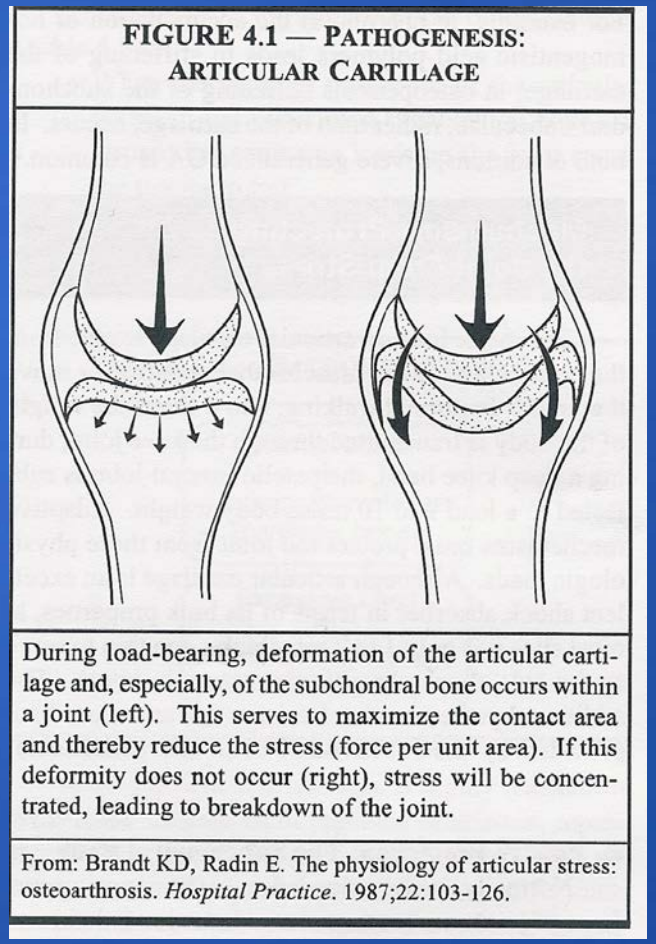
#1- Osteoarthritis

#2- Osteoporosis

#3- Oop's I peed my pants!

Pathophysiology of Osteoarthritis

- Failure of articular cartilage
- Hyaline cartilage is composed of:
  - Matrix- providing tensile & compressive strength.
  - Chondrocyte- synthesize & maintain matrix
    - - Collagen
    - - Proteoglycans

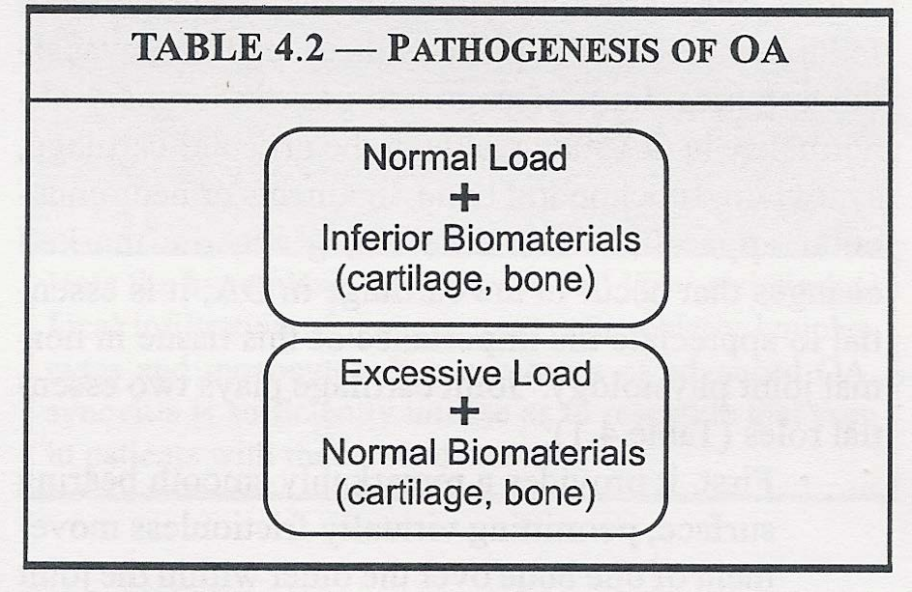


Pathophysiology of Arthritis

- Mankin Theory (older- Traditional)
  - 2 types of injuries to the cartilage:
    - 1) Superficial- no extension into the subchondral bone
    - 2.) Deep - into the subchondral surface-
      - Produces fibro cartilage

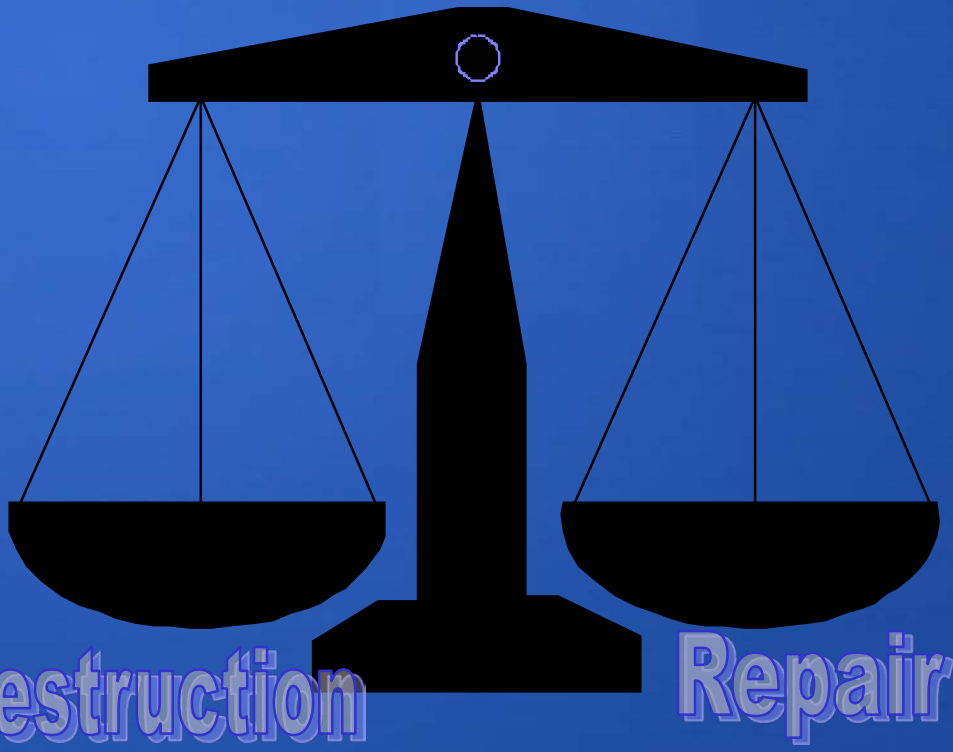
Pathophysiology of Arthritis

- Radin Theory
  - Impact Injuries
    - Multiple traumas to the area exceeds the normal repair threshold



Causes of Degenerative Arthritis

- When your ability to repair the multiple daily injuries to your cartilage is more than your body's ability to repair the injury

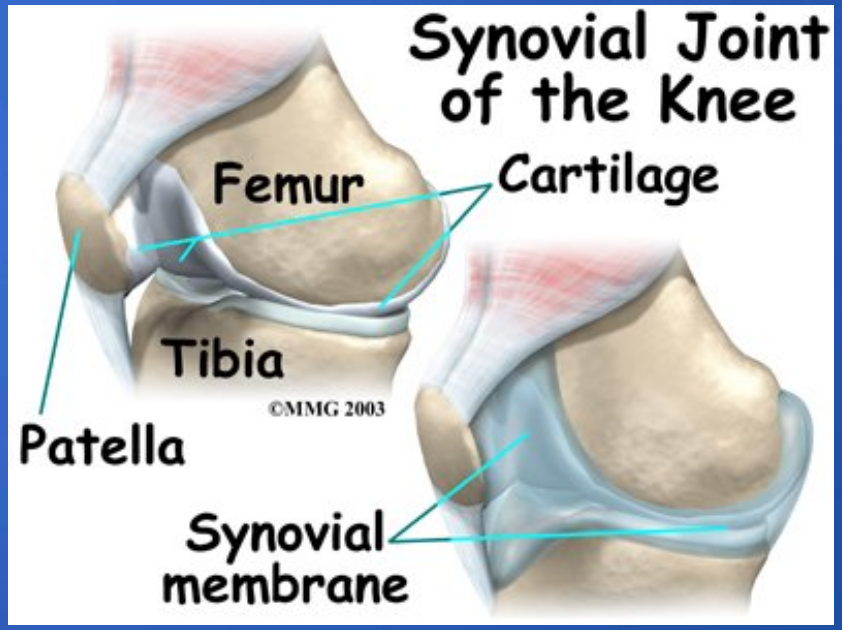


Homeostasis

- Is the property of a system, that regulates its internal environment and tends to maintain a stable, constant condition.
- Example: Big Macs and Myocardial Infarction.

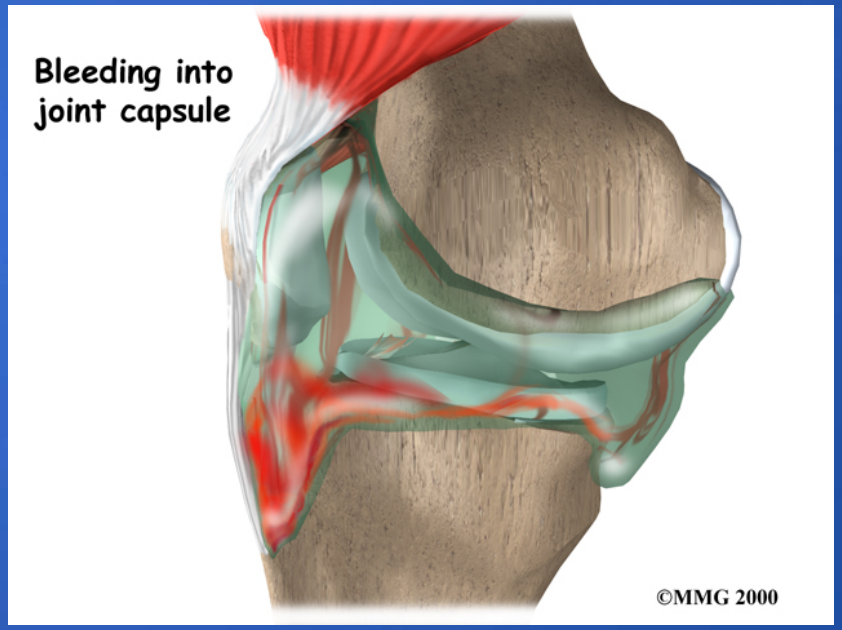
Pump Theory of Arthritis

- No blood supply to articular cartilage
- Synovial fluid motion is analogous to blood flowing to the heart.
- Cartilage metabolizes normally when the pump is working well.



Pump Theory of the Knee

- Interruption of synovial fluid movement by:
  - immobilization,
  - meniscal or ligament injury,
  - changes in synovial fluid viscosity
  - Malalignment
- Cause destruction of the cartilage.



Goals of Treatment of Arthritis

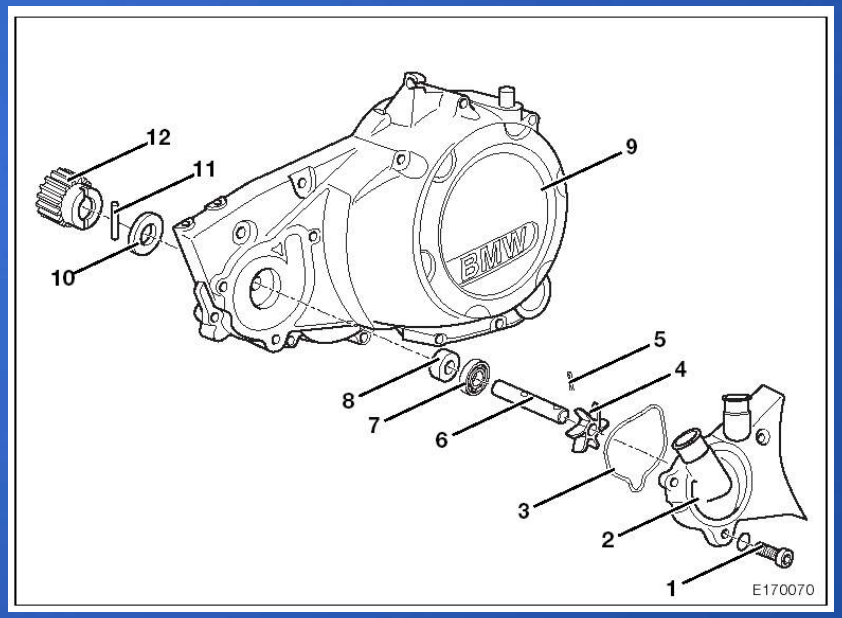
- Get the Pump Moving
- Reduce Destruction
- Improve alignment of the pump
- Stimulate Repair
- Educate patients and families to take charge and participate in their health care.

Getting the Pump Moving

- Fact #1:Joints that don't move get worse.
- Fact #2: Controlled, safe motion helps joints heal.
- Fact #3:Exercise reduces feelings of depression.

Getting the Pump Moving

- Inactivity Of Joints Causes
  - Decreased production of proteoglycans
    - (Howell et al: Primer on Rheum. 1988)
  - Decreased Type II B Muscle Fibers
    - (Dantzig et al. Textbook of Rhem, 1993)
  - Social Isolation
    - (Yelsin et al: J. Rheum, 1987)



Exercise
The Good; The Bad & The Ugly

- Good- Low impact aerobic exercise
  - 80 pts randomized, controlled study-12 wks of aquatics & ROM - showed improved 50 ft walk, less depression & anxiety<.05) for up to 9 months (Minor: Arthritis & Rheum, 1989)
- The Bad- Repetitive high impact exercise
  - Strenuous exercise causes decrease in proteoglycan synthesis as compared to moderate exercise programs (p<.05) up to 16 weeks after program stopped (Little: Osteoarthritis Cartilage; 1997)
- The Ugly- Stop & Go sports/activities
  - Maximum isometric exercise and standing exercises produced highest hip pressures on in vivo pressure monitoring (Tackson; Arthritis Care Res. 1997)

Quadriceps Strengthening

- Randomized, Controlled Study of 61 pts
  - Diathermy & 200 leg extensions vs. diathermy alone
  - Leg extension group improved on Bandi Score ($p<.01$) & Strength ($p<.01$)
  - (Jan et al: Forms Med Assoc., 1993)

Quadriceps Mystery

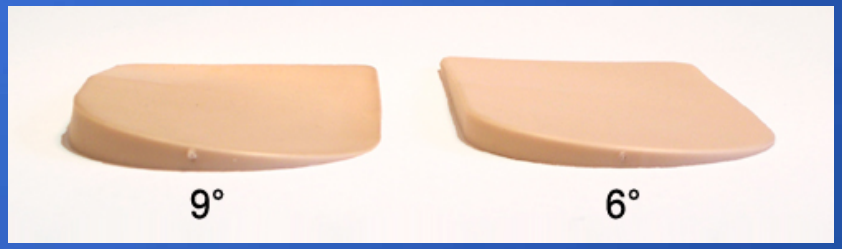
- Randomized, Cross Educational Study of 462 patients
- Patients with measurable quad weakness had a higher risk for OA
- " May be a reflex phenomenon & not atrophy causing this"
  - (Selmenda et al: Ann Int Med, 1997)
- What could this reflex phenomenon mean?

Osteopathic Manipulative Therapy

- Gentle Manipulation stimulating muscle afferents & efferents through a reflex phenomenon.
- Controlled prospective animal study
  - Animal model receiving OMT showed improved histological results (Escabedo et al:NYCOM, AOA 41st Res Conf, 1997)

Correcting the Pump Alignment

- Controlled, retrospective study of 85 pts, 121 knees
  - 1/4" lateral heel wedge for varus OA
  - At 12 months- 88% reported excellent or good pain relief on HSS (Keating et al:Ortho Review, 1993)
- Simple ACE Wrap improves Proprioception & feeling of stability (McNair PJ et al: Arch Phys Med Rehab, 1996)

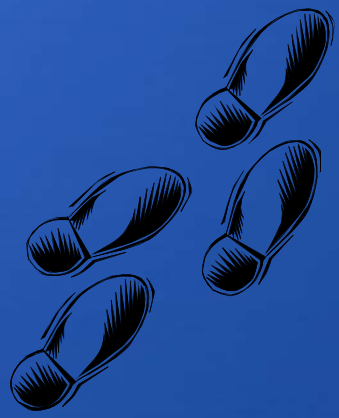


Correcting the Pump

- Unloader Bracing
- Recommendation reported by the Osteoarthritis Research Society International in the ability of off-loader knee braces to reduce pain, improve stability, and diminish the risk of falling was 76% (95% confidence interval, 69%–83%)

Joint Protection (Reducing Destruction)

- Wear Proper Shoes
- Every step causes pressure and shearing across joints
  - Proper shoe wear can reduce joint loading by 800%
- Stable shoes help reduce these forces
  - High heels cause 23% increased torque (Kerrigan et al:Lancet, 1998)



Joint Protection

Anatomy of Shoe Wear

- Shock Absorbing Soles- PUSH

- Strong Shank – TWIST

- Stabilizing Heel Cup- SQUEEZE

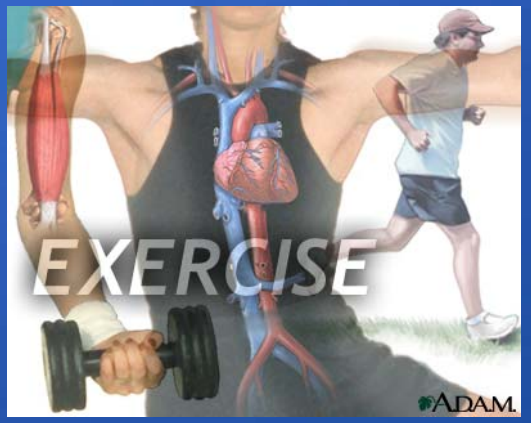
Good Box,
Bad Box

Weight Reduction (Reducing Destruction)

- Every extra pound of weight produces over 4 million pounds per leg per year.
- The risk for knee OA increased by 36% for every 2 units of BMI (5 kg) of weight gain. (March et al; Med J Aust. 2004; 180)
- Obesity resulted in a hip replacement 10 yrs earlier and knee replacement 13 yrs earlier than non-obese patients. (Changulani M; JBJS Br. 2008; 90 (3):360-3)
- Reducing only 5% of total body weight at 0.24% per week significantly reduced pain and disability scores (Christensen R; Ann Rheum Dis. 2007;66(4):433-9)

Combining Weight Reduction and Exercise

- Will the age old recommendation of diet and exercise reduce arthritic symptoms better than one alone?
- ADAPT (Arthritis Diet & Activity Promotion Trial) – 18 months of calorie restriction and exercise resulted in 24 % improvement in physical function and 30.3% reduction in knee pain compared to diet or exercise alone.



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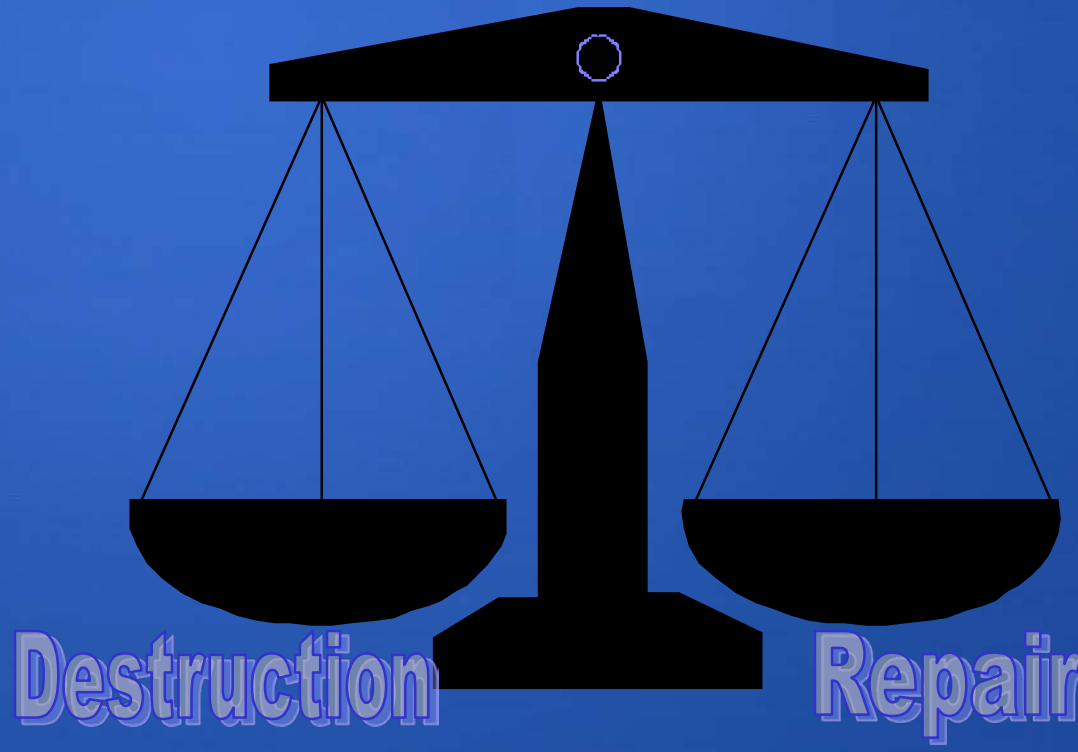
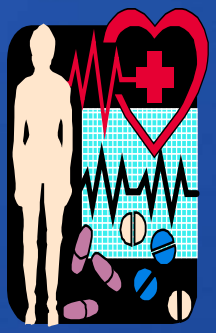


Joint Repair

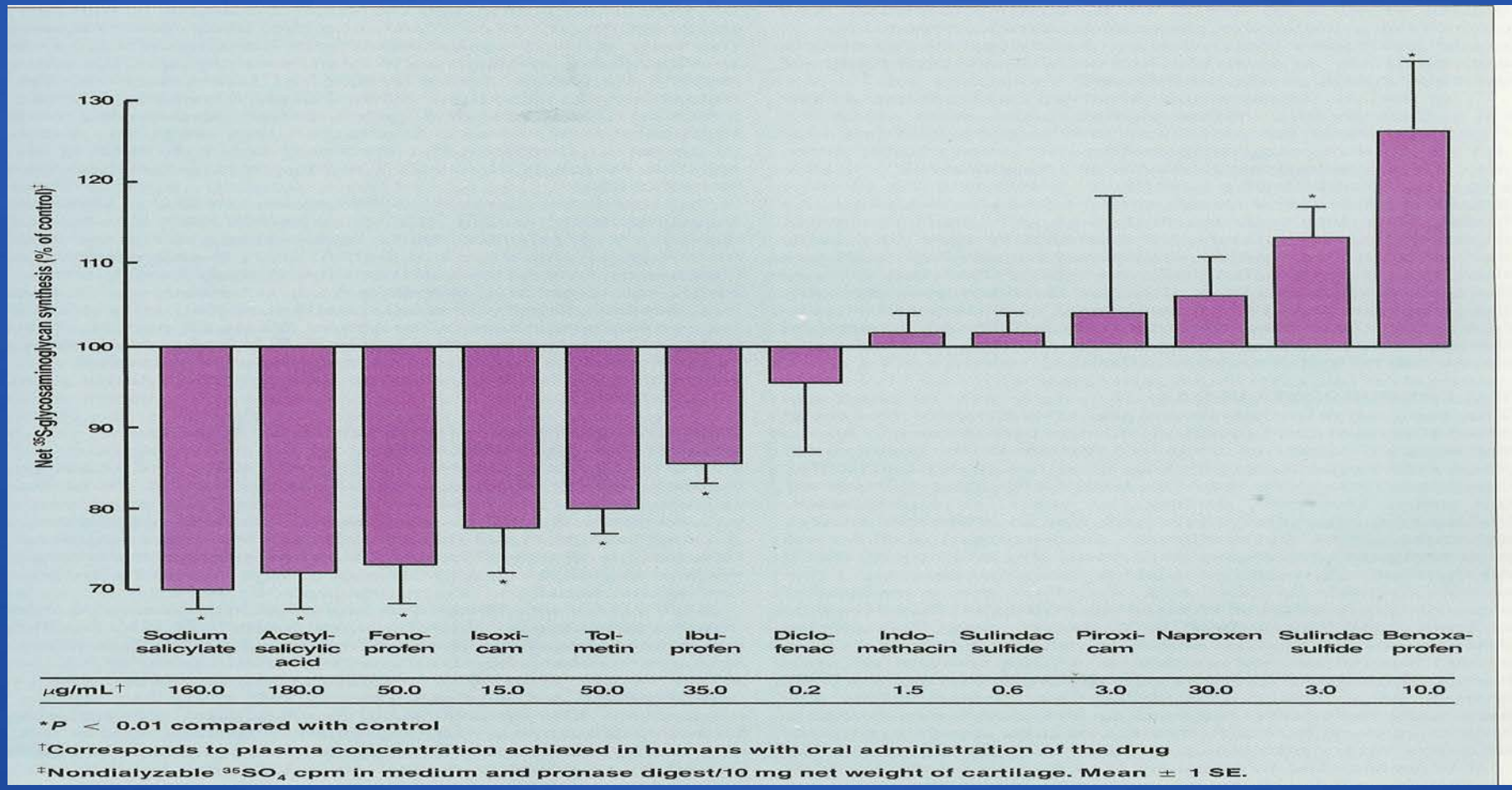
- Principles of Joint Repair:
  - Optimize the patient's body to heal by reducing pain without harming the body.
  - Optimize nutrition to provide joint with elements needed for repair.
  - Stimulate the joint to reduce destruction AND stimulate cartilage production.

Optimize the patient's body to heal by reducing pain without harming the body

- Allowing patients to understand what , when & why they take their medications:
  - Improves compliance & eliminates duplicate meds
- Selective use of NSAIDS for OA
  - NSAIDS may inhibit proteoglycan synthesis(Brandt; Am J. Med,1987)
  - Acetaminophen as effective in reducing pain of OA as compared to high doses of Ibuprofen with significantly reduced side effects (Bradley: J. Rheum, 1992)



NSAID Effect on net S-glycosamineglycan synthesis



*P < 0.01 compared with control

†Corresponds to plasma concentration achieved in humans with oral administration of the drug

‡Nondialyzable $^{35}SO_4$ cpm in medium and pronase digest/10 mg net weight of cartilage. Mean ± 1 SE.

Optimize the patient's body to heal by reducing pain without harming the body

- Topical Analgesics- Capsaicin-P
- Very effective , low cost, low side-effects
- Randomized, double-blinded controlled study of 70 pts
  - Significant improvement in pain score (p=.002)

Optimize nutrition to provide joint with elements needed for repair.

- Nutrition-Micronutrients
  - Antioxidants- Vitamins C, E, Bioflavonoid
    - Vitamin C- 640 subjects, retrospective review
      - Subjects taking vitamin C had slower progression of OA on radiographs (McAlindon et al.: Arth Rheum, 1996)
    - Vitamin E- Inhibits breakdown & stimulates GAG
      - (Machtey, Geri. Soc, 1978)
    - Bioflavonoid- gives fruit color and makes tea green
      - Reduces destruction of collagen (Tixier: Biochem Pharm, 1984)
      - Reinforces cross-linking of fibers (Masquelier: Acta Ther,1981)

Optimize nutrition to provide joint with elements needed for repair.

- Micronutrients- Boron, Essential Fatty Acids
  - Boron- found in apples, cauliflower
    - Epidemiologic studies show intake < 1 mg/day = 20-70% incidence of OA, intake of 3-10mg/day= 10% incidence (Environmental Health Prospective, Nov. 1994)
  - Essential Fatty Acids- Omega 3
    - Reduces series 2 prostaglandins & arachidonic acid
    - 64 patients taking 10 Max EPA/day had significant reduction in pain & need for meds. (Lau: Br. J. Rheum, 1991)

Optimize nutrition to provide joint with elements needed for repair.

- Vitamin D- Found in cold water fish, butter, eggs
  - A Genetic Link?
  - 2.82 fold increase of risk with one VDR haplotype and development of radiographic evidence of OA(Keen: Arthritis Rheum, Aug 1997)
  - 556 pts. In Framingham study evaluated for correlation between levels of Vitamin D and progression of arthritis-
    - Lower levels of serum vitamin D in women had a threefold increase in progression of arthritis (McAlindon: Ann Int Med, 1996)

Stimulate the joint to reduce destruction AND stimulate cartilage production

- Chondroprotective Agents
- Definition- Chondroprotective
  - 1.) Block the progression of degradation Or
  - 2.) Stimulate repair of cartilage
- Types:
  - Blockers: Doxycycline, Hyluronate, Chondroitin
  - Stimulators: Glucosamine, Hyluronate, Chondroitin
  - Mechanical : (combination blockers/ stimulators) CPM, Ultrasound, PEMF, Exercise, Vibration

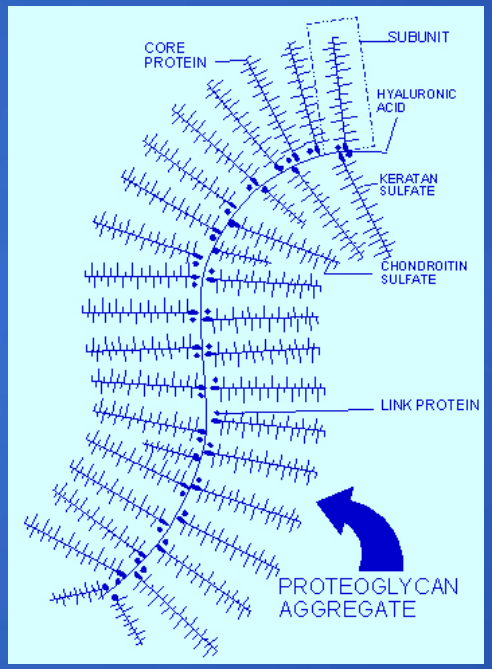
Cartilage Cell

- Glycosaminoglycans

  Hyluronic Acid- Central Core
- Proteoglycan Complex

  Keratin Sulfate

  Chondroitin Sulfate



Stimulate the joint to reduce destruction AND stimulate cartilage production

- Glucosamine Sulfate
  - Made from covering of shellfish (chitin).
  - Well absorbed through stomach and into joints.
  - Stimulates glycosamineglycan to produce more cartilage.
  - Provides minimal reduction of inflammation.
  - Main effect may be sulfur donation from sulfate.
  - Other forms: Glucosamine HCL, Glucosamine NAS may **not** be as effective.
  - Needs at least two months to work.

Stimulate the joint to reduce destruction AND stimulate cartilage production

- Review of 13 double-blinded, placebo-controlled trials of greater than 4 weeks-
  - Glucosamine sulfate had a statistically significant ($p<.05$) ability to reduce pain and symptoms of joint pain as compared to a placebo or NSAID in all 13 studies.

    (Deal; Rheum Dis Clinics North Am, 1999)
- Explaining limited effect of NIH Study-
  - Used Glucosamine HCL **without** a sulfur donor.

Cartilage Cell

- Glycosamineglycan
  - Hyluronic Acid- Central Core
- Proteoglycan Complex
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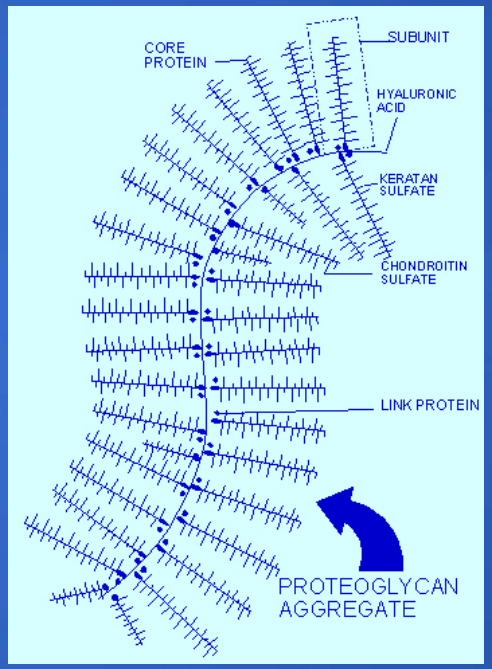
  - Chondroitin Sulfate



Stimulate the joint to reduce destruction AND stimulate cartilage production

- Micronutrients- Chondroitin Sulfate
  - Potentially provides hydrophilic character to GAG complex.
  - May inhibit enzymes causing cartilage degradation.
  - Meta-analysis of 12 published trials shows:
    - Only 4 were fitting criteria and all 4 showed statistically significant ($p<.05$) improvement as compared to placebo or NSAID. (Deal; Rheum Dis Clinics North Am, 1999)

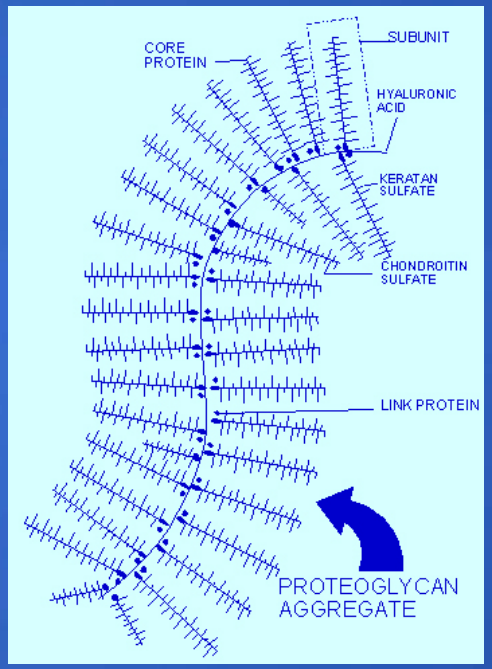
Cartilage Cell

- Glycosamineglycan

  Hyluronic Acid- Central Core

  Proteoglycan Complex

  - Keratin Sulfate
  - Chondroitin Sulfate



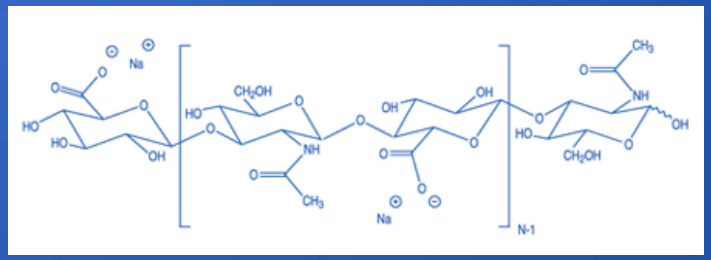
Stimulate the joint to reduce destruction AND stimulate cartilage production

- **Hyluronate**
  - Central core of proteoglycan.
  - Important in maintaining the viscosity of synovial fluid.
  - Easily broken down in early OA.

Potential Uses for HA

- *note- not all applications are FDA approved:
- Ophthalmology
- Soft tissue implants
- Wound healing
- Viscosupplementation of joints
- Bone regeneration
- Surface coatings

- Moisturizing agents
- Adhesion prevention
- Cell preservation
- Drug delivery
- Immunomodulation



Hyluronic Injections for Dermatology

- Hyluronic injections for Wrinkles

Stimulate the joint to reduce destruction AND stimulate cartilage production

- 495pts, controlled, prospective, randomized, double-blinded study-
  - 56% of pts receiving Hyluronate had pain relief for 6 months & improved function with less side effects (2% vs. 9%) as compared to Naprosyn.
- May induce cartilage healing
  - Controlled, rabbit study of induced OA
    - One knee injected w/ saline other w/ Hyluronate. Hyluronate knees showed evidence of cartilage healing.
- May delay need for TKR
  - 11187 knees injected with HA. 75% of patients with grade 4 changes had not undergone TKR at 3.8 yrs. (Waddell et al; AAOS 2005 Abstract)

Doxycycline

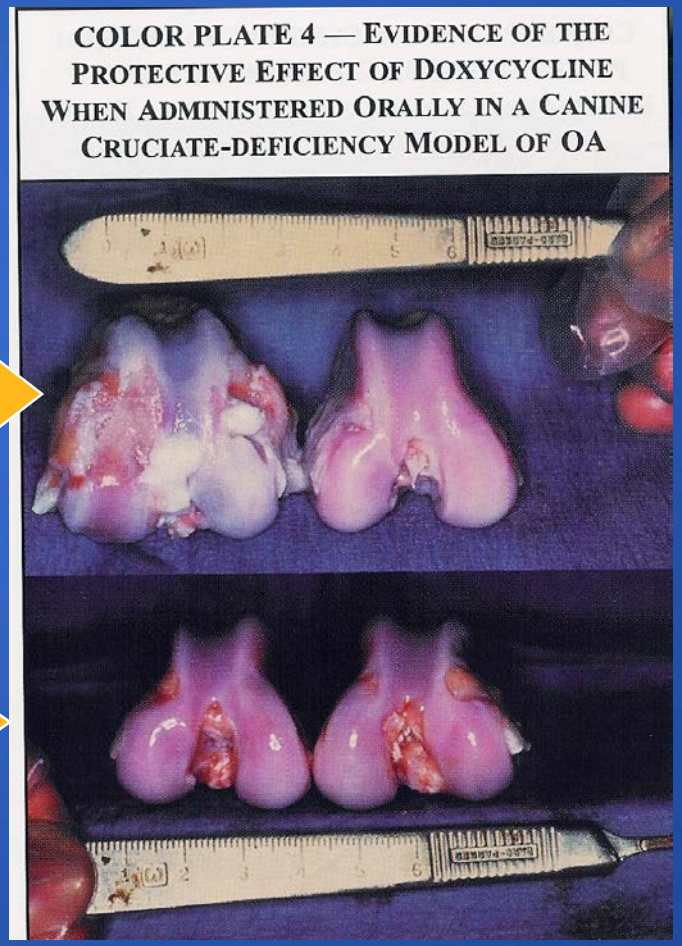
- Over 20 years of safe use.
- Prevents enzyme that breaks down cartilage.
- Inhibits:
  - Matrix metalloproteinase (MMP) enzymes.
  - Changes in Chondrocyte phenotype found in early OA.
  - Inhibit the expression of nitric oxide synthetase (NOS).
- In-Vitro, controlled canine ACL deficient model
  - The group given oral doxy had normal appearing cartilage as compared to the untreated group.

Doxycycline

- Canine ACL deficient Models given Doxycycline (3.5 mg/kg).

Control

Doxycycline



Mechanical Stimulants

Magic- 30 Hz

Mechanical Stimulants

- Continuous Passive Motion (CPM)
  - Motion of synovial fluid and even loading of surface stimulates earlier onset of healing
    - Effective for defects less than 3 mm in diameter (O' Driscoll, Keeley and Salter, JBJS 68-A: 1017-1035, Sept. 1986)

Effective range is 30 hz.

Mechanical Stimulus

- Pulsed Electromagnetic Field (PEMF)
- Electromagnetism holds all atoms together and allows chemistry to work.
- Loading of tissue produces piezoelectric fields in dry tissue and streaming potentials in fluids or moist tissue.
- Disease interrupts the normal fields.
- PEMF re-establishes normal physiologic loading fields.

Mechanical Stimulation- PEMF

- Gated (pulsed) waveforms alternating high frequency (1-10 kHz) and low (1-100kHz) allow capacitors placed on the skin to penetrate to the tissue below and mimic impact loading .
- Other Mechanisms of PEMF
  - Electromagnetic fields increase Insulin like growth factor II receptor translation or the factor itself.

Most effective range is 15-30 Hz .

Mechanical Stimulants

- Pulsed Electromagnetic Field(PEMF)

Mechanism of Action of Pulsed Signal Therapy

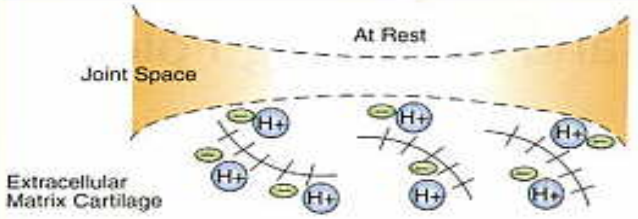


FIGURE 1. At rest, an equilibrium exists between hydrogen protons and negative charges in the extracellular cartilage matrix, and there is no streaming potential.

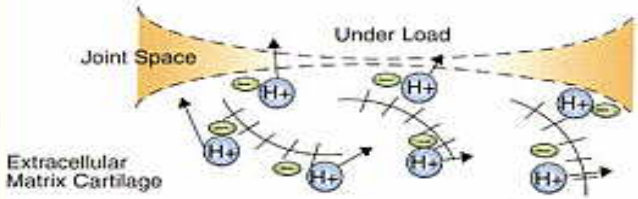


FIGURE 2. When the joint space is compressed as a result of physical pressure, a streaming potential is created as fixed negative charges in fluid forced out of cartilage cause hydrogen protons to move into the joint space.

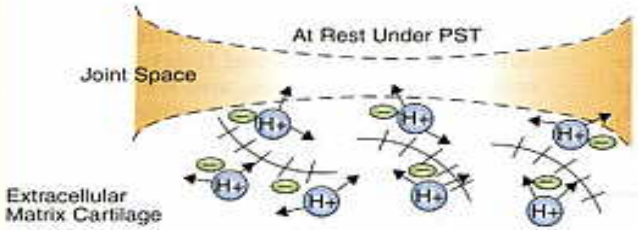


FIGURE 3. A similar streaming potential can be generated in the resting state by PST. This is due to the forced movement of hydrogen protons which results in alternating energies stimulating chondrocytes in matrix connective tissue.

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Results of PEMF

- PEMF Results using Pulsed Signal Therapy (PST)
- Controlled, double-blinded, randomized US Study
  - 81 Pts with OA of the knee and 86 OA of C-Spine
  - Statistically significant decrease in pain scores, pain on motion and global assessment.
    - (Trock, J Rheumatology 1994; 21(10): 1903-1911)
- 130% improvement over placebo in the Physician Global Evaluation, a 120% improvement over placebo in the Patient's Evaluation of Pain and Symptoms. In a addition, patients were 2/3rds less likely to have a total knee replacement. (Mont MM, Hungerford DS et al Orthopedics. October 2006; 29(10): 887-892.)

Whole Body Vibration (WBV)

- Previously used by *Charcot* to resolve migraine headaches and *John Harvey Kellogg* to build muscle wellness with vibrating chairs, bars and platform.
- *Vladimir Nazarov* developed a hand held device for prevention of muscle and bone atrophy for the Russian Space Institute.
- Used by many athletes such as Lance Armstrong and celebrities such as *Madonna* to improve physical stamina.

Whole Body Vibration

- How it works
  - The plate moves up and down in the vertical (‘z’) axis at between 25-30 Hz rate while standing.
  - This vibration frequency stimulates the Involuntary Muscle Stretch Reflex(IMSR) causing up to 1,500 muscle contractures per minute.

25-30 Hz

[Excercise for Patients with Incontinence]

Whole Body Vibration

- What are the results?
  - *Improvement of muscle power after Galileo training (upper picture, Bosco, in: Clin. Physiol. 1999), improvement of sprint speed, agiligy and jump height in comparance to explosive weight training (Berschin, in: Leistungssport 2003)*
  - 27 Total Hip Patients- The whole-body-vibration group scored a mean of 0.05% higher on the Sensory Organization Test, 39 watts higher on the Bassey Power Rigg test, and 1.99 seconds faster on the Timed Get Up and Go test; all between-group differences were statistically significant ($P < .05$).

Whole Body Vibration

- Further Studies:
  - Osteoporosis and Balance- BMD in the WBV group increased by 4.3% (*P* = .011), but there was no effect on lumbar spine BMD in either group. In the WBV group only, balance improved by 29% (Gusi N, BMC Musculoskelet Disord. 2006;7:1-8)
  - Incontinence - average grade of stress urinary incontinence decreased. These results were also reflected by a subjective improvement of complaints in all patients (p < 0,001). (Von der Heide S,. EFFECT ON MUSCLES OF MECHANICAL VIBRATIONS PRODUCED BY THE GALILEO 2000 IN COMBINATION WITH PHYSICAL THERAPY IN TREATING FEMALE STRESS URINARY INCONTINENCE)

30 Hz treats the 3 O's of Getting Older

Platelet Rich Plasma (PRP)

- PRP- Taken from patient's own blood (usually 10-60 cc)
- Cells are separated in solution usually through centrifuge into platelet rich plasma (PRP) and platelet poor plasma (PPP)
- PRP contains increased growth factors and ability to reduce production of MMP enzyme.

PRP for Arthritis

Filardo G; Kon E; et al.; Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis; Knee Surg SportsTraumatol Arthrosc; 2010 Aug 26

- Retrospective study of 90 patients treated with three injections of PRP into arthritic knees at 24 month follow up. All of the parameters at the 24 month period improved including the IKDC subjective and objective parameters for a median length of improvement for over 9 months.

PRP for Arthritis

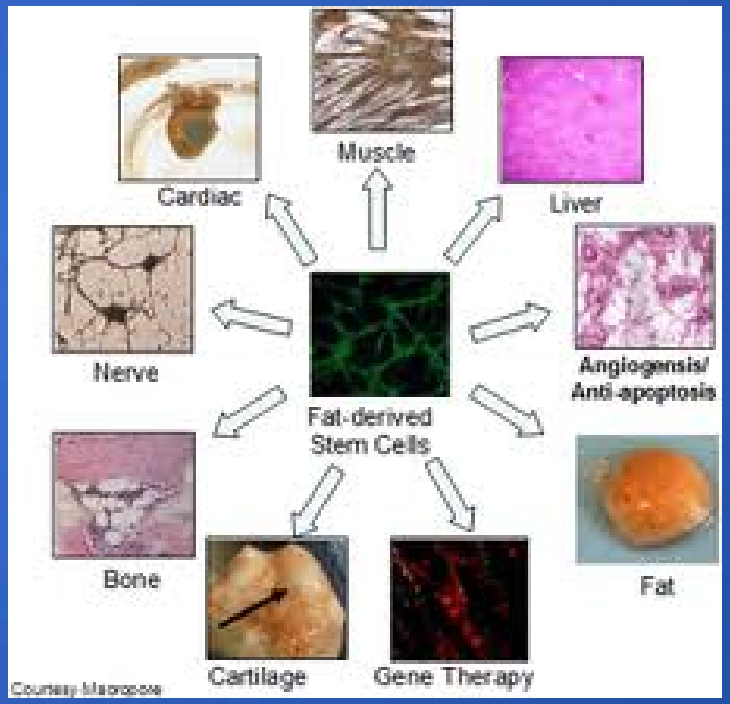
- Kon E, Buda R et al: Platelet Rich Plasma ; Intra-articular injections produced favorable results on degenerative cartilage lesions. Knee Surg Sorts Traumatol Arthrosc. 2010 Apr; 18(4): 472-9
- • Prospective study of 100 consecutive patients with osteoarthritis of the knee injected 115 knees with 3 cc of platelet rich plasma and followed at 6 and 12 months with the IKDC and the EQ VAS . Statistically significant improvement was seen with $p < 0.0005$ from baseline at 6 months but did worsen at 12 months ($p = 0.02$). Authors conclude that PRP is safe and has the potential to reduce pain and improve knee function.

PRP vs HA

- Sanches M; Anitua E.; Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study; Clin Exp Rheumatol; 2008, Sept-Oct: 26(5); 910-3
- • Retrospective, controlled study in human knees with known OA comparing hyluronic injections to PRP. 3 injections were given one week apart over 3 weeks. At 5 weeks, the PRP group had reduced pain scales by 33.4% compared to the HA group reduction of only 10%.

Adipose Derived Stem Cells

- This is NOT fetal derived stem cells but rather adult from your own fat.
- Adipose (fat) cells of the abdomen have the highest concentration of adult stem cells.
- Stem cells can form many different types of tissue if they are induced properly.



Adipose Derived Stem Cells

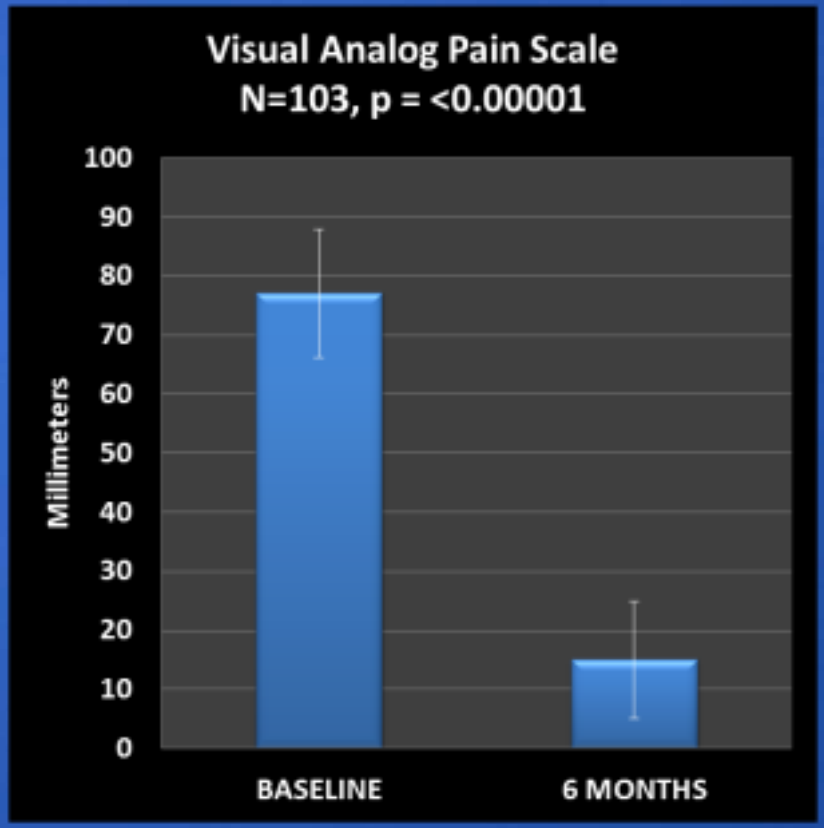
- Adipose tissue taken from the abdomen can be used to concentrate viable adult stem cells into a specific area of disease.

Ageless IRB Study for Arthritis of the Knee

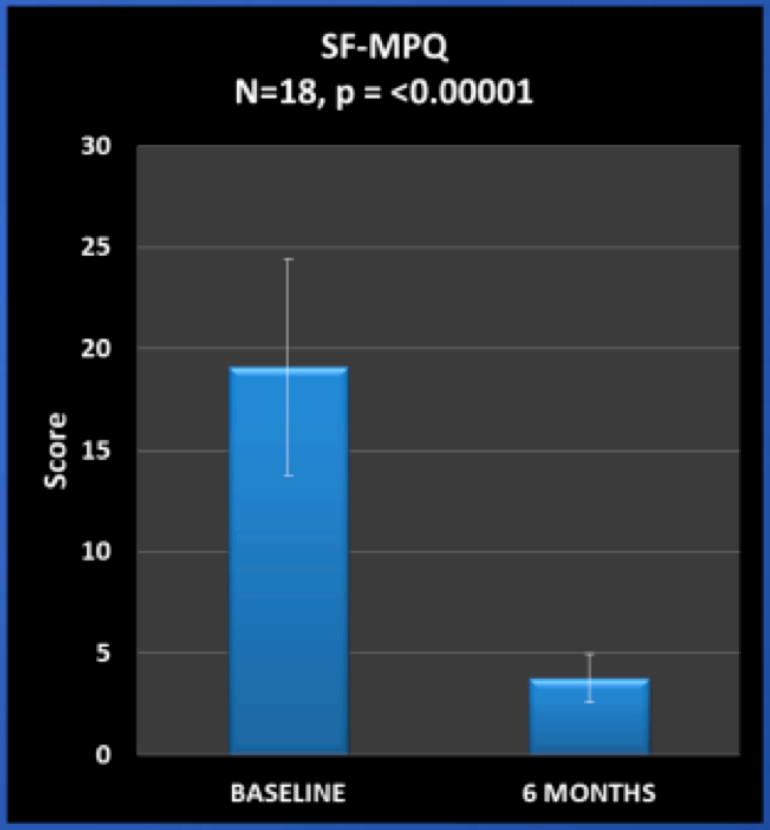
- 55 active sites enrolling
- 6 months follow up
  - Adverse Events
  - Short Form McGill Pain Questionnaire (SF-MPQ)
  - Visual Analog Score (VAS)
  - Present Pain Inventory Score (PPI)

Ageless IRB Study for Arthritis of the knee

- 103 patients collected
- 3 clinical sites
- 75% average improvement over baseline
- Statistically significant (p=<.00001) reduction in pain from baseline .

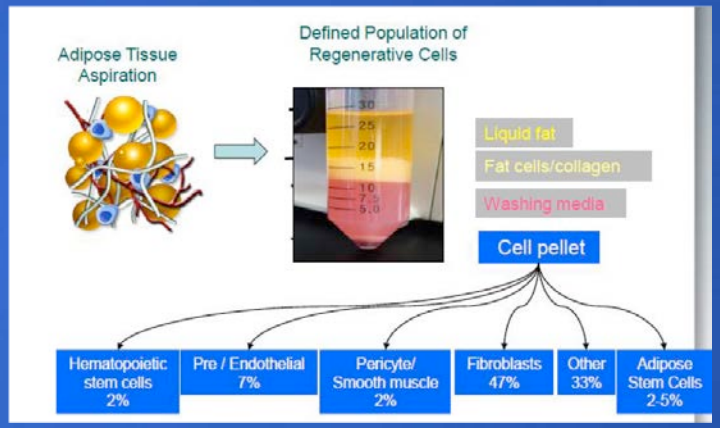


- Only 18 patients from 3 sites
- Statistically significant reduction in McGill Pain Questionnaire (p=<.00001)
- Average 75 % reduction in pain scores.



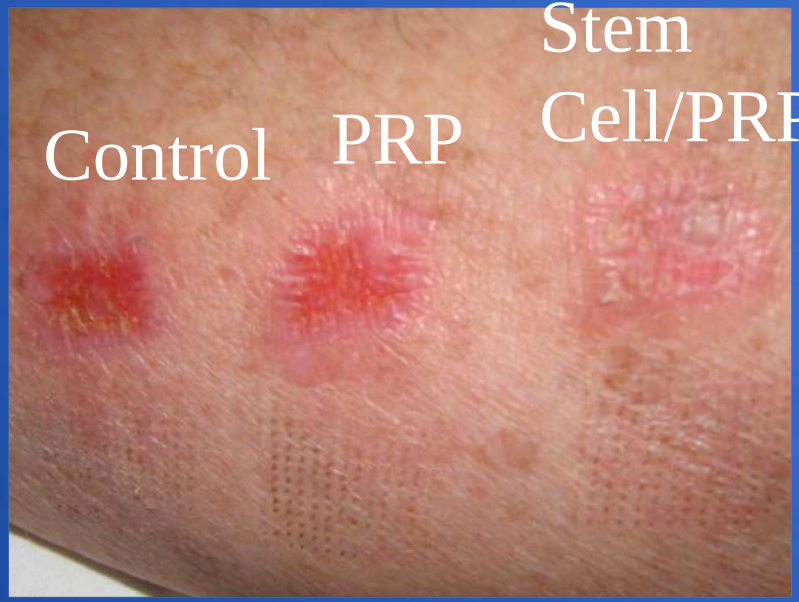
Ageless IRB Study for Arthritis of the knee

- Limitations-
  - Very small sample
  - Short term follow up
  - Does not correct mechanical malalignment , laxity of ligaments or mechanical instability of the joint

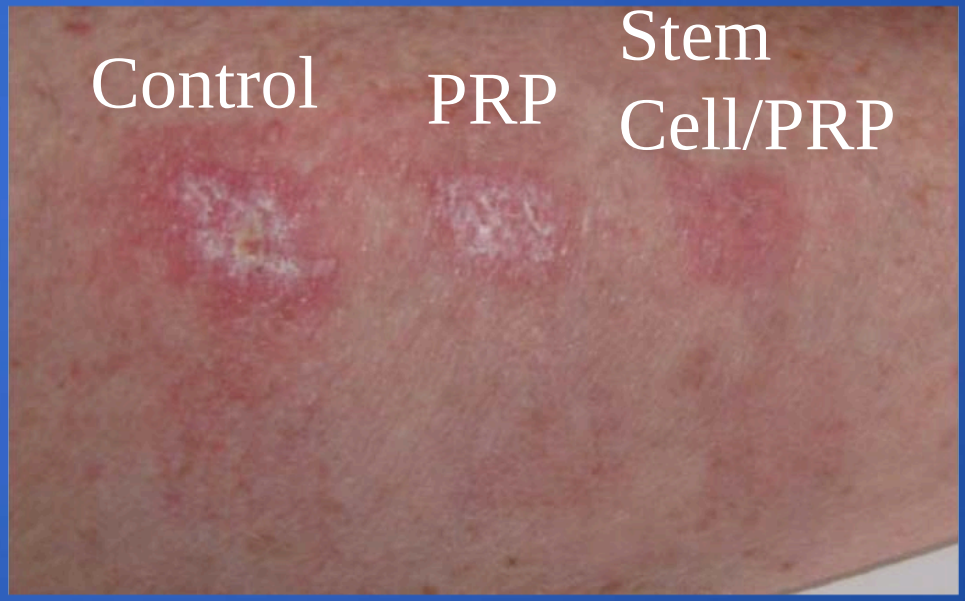


PRP vs Stem Cell

DAY #6



DAY #14



2 year follow up of adipose derived stem cell treatment

30 elderly patients over the age of 65.

Followed for 2 years

All 30 had improvement in function and reduction of pain

No patients went on to a total knee

All patients improved progressively from year 1 to 2.

No adverse side effects.

Knee Surg Sports Traumatol Arthrosc
DOI 10.1007/s00167-013-2807-2

KNEE

Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis

Yong-Gon Koh · Yun-Jin Choi · Sae-Kwang Kwon · Yong-Sang Kim · Jee-Eun Yeo

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Abstract

Purpose In the present study, the clinical outcomes and second-look arthroscopic findings of intra-articular injection of stem cells with arthroscopic lavage for treatment of elderly patients with knee osteoarthritis (OA) were evaluated.

Methods Stem cell injections combined with arthroscopic lavage were administered to 30 elderly patients (≥65 years) with knee OA. Subcutaneous adipose tissue was harvested from both buttocks by liposuction. After stromal vascular fractions were isolated, a mean of 4.04×10^6 stem cells (9.7 % of 4.16×10^7 stromal vascular fraction cells) were prepared and injected in the selected knees of patients after arthroscopic lavage. Outcome measures included the Knee Injury and Osteoarthritis Outcome Scores, visual analog scale, and Lysholm score at preoperative and 3-, 12-, and 2-year follow-up visits. Sixteen patients underwent second-look arthroscopy.

Results Almost all patients showed significant improvement in all clinical outcomes at the final follow-up examination. All clinical results significantly improved at 2-year follow-up compared to 12-month follow-up ($P < 0.05$). Among elderly patients aged >65 years, only five patients demonstrated worsening of Kellgren–Lawrence grade. On second-look arthroscopy, 87.5 % of elderly patients (14/16) improved or maintained cartilage status at least 2 years postoperatively. Moreover, none of the patients underwent total knee arthroplasty during this 2-year period.

Conclusion Adipose-derived stem cell therapy for elderly patients with knee OA was effective in cartilage healing, reducing pain, and improving function. Therefore, adipose-derived stem cell treatment appears to be a good option for OA treatment in elderly patients.

Level of evidence Therapeutic case series study, Level IV.

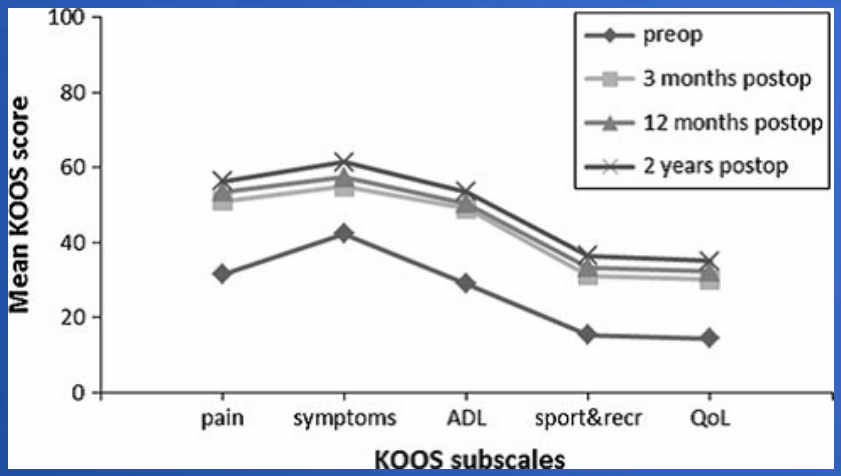
Keywords Mesenchymal stem cell · Arthroscopic lavage · Knee osteoarthritis

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder [3]. Synovial inflammation, in particular, can affect joint homoeostasis [5] and is associated with pain and OA disease progression [31]. The current treatments for OA are not regenerative and have little impact on the progressive degeneration of joint tissues. Clinical interventions are primarily symptomatic and focus on pain reduction and inflammation control through nonsteroidal anti-inflammatory drugs and ultimately with total joint replacement [4]. Few options are currently available for elderly patients with moderate to severe arthritis. Most approaches are palliative and address symptoms rather than influencing the biochemical environment of the joint or disease process.

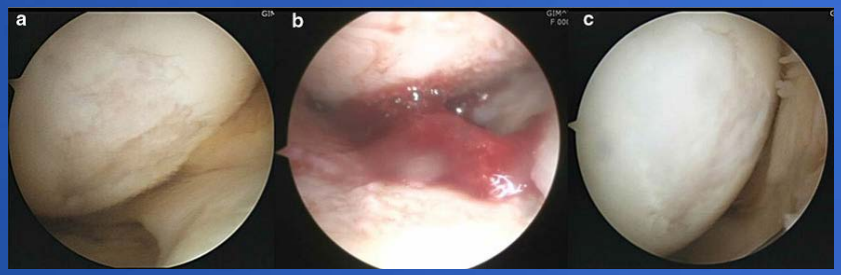
Because of their multilineage potential, immunosuppres-

2 year follow up



- 2 year follow up on KOOS scores.
- Note- progressive improvement over 2 year period in all parameters including sports and recreation.

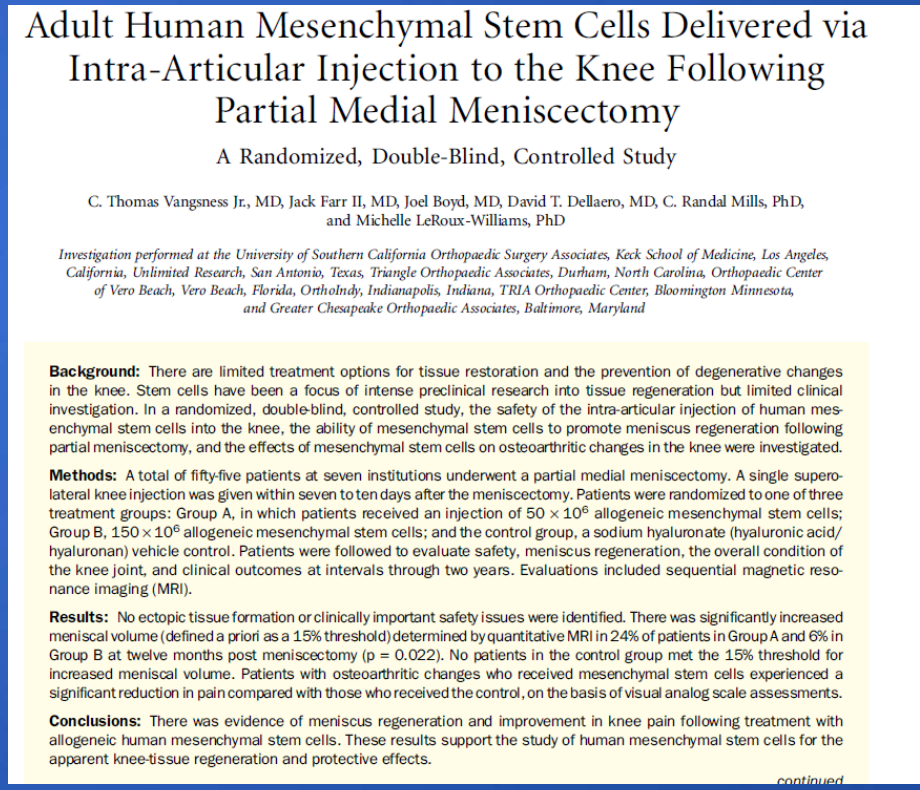
Second Look Arthroscopy



- Second look on 16 of 30 patients
- Positive cartilage change in 62.5% , neutral in 25% and negative in 12.5%

JBJS Stem Cell Injection Following Partial Menisectomy

- RCT OF 25 patients with meniscal tears.
- Received either HA (Supartz) or allogenic (from someone else) injection of mesenchymal stem cells
- Followed for 2 years with MRI every 6 months and VAS
- 24% of patients grew more than 15% of new meniscus tissue
- Patients with OA of the knee had significant relief of pain compared to the HA injection.



Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy

A Randomized, Double-Blind, Controlled Study

C. Thomas Vangsness Jr., MD, Jack Farr II, MD, Joel Boyd, MD, David T. Dellaero, MD, C. Randal Mills, PhD, and Michelle LeRoux-Williams, PhD

Investigation performed at the University of Southern California Orthopaedic Surgery Associates, Keck School of Medicine, Los Angeles, California, Unlimited Research, San Antonio, Texas, Triangle Orthopaedic Associates, Durham, North Carolina, Orthopaedic Center of Vero Beach, Vero Beach, Florida, Ortholndy, Indianapolis, Indiana, TRIA Orthopaedic Center, Bloomington Minnesota, and Greater Chesapeake Orthopaedic Associates, Baltimore, Maryland

Background: There are limited treatment options for tissue restoration and the prevention of degenerative changes in the knee. Stem cells have been a focus of intense preclinical research into tissue regeneration but limited clinical investigation. In a randomized, double-blind, controlled study, the safety of the intra-articular injection of human mesenchymal stem cells into the knee, the ability of mesenchymal stem cells to promote meniscus regeneration following partial meniscectomy, and the effects of mesenchymal stem cells on osteoarthritic changes in the knee were investigated.

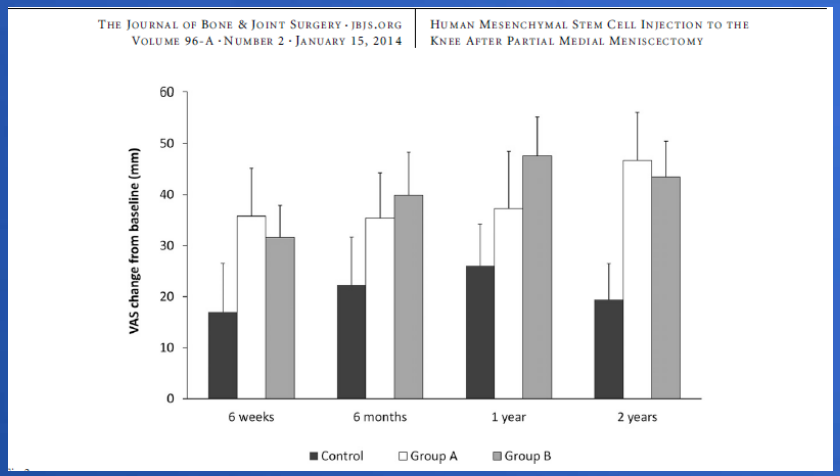
Methods: A total of fifty-five patients at seven institutions underwent a partial medial meniscectomy. A single superolateral knee injection was given within seven to ten days after the meniscectomy. Patients were randomized to one of three treatment groups: Group A, in which patients received an injection of 50×10^6 allogeneic mesenchymal stem cells; Group B, 150×10^6 allogeneic mesenchymal stem cells; and the control group, a sodium hyaluronate (hyaluronic acid/hyaluronan) vehicle control. Patients were followed to evaluate safety, meniscus regeneration, the overall condition of the knee joint, and clinical outcomes at intervals through two years. Evaluations included sequential magnetic resonance imaging (MRI).

Results: No ectopic tissue formation or clinically important safety issues were identified. There was significantly increased meniscal volume (defined a priori as a 15% threshold) determined by quantitative MRI in 24% of patients in Group A and 6% in Group B at twelve months post meniscectomy ($p = 0.022$). No patients in the control group met the 15% threshold for increased meniscal volume. Patients with osteoarthritic changes who received mesenchymal stem cells experienced a significant reduction in pain compared with those who received the control, on the basis of visual analog scale assessments.

Conclusions: There was evidence of meniscus regeneration and improvement in knee pain following treatment with allogeneic human mesenchymal stem cells. These results support the study of human mesenchymal stem cells for the apparent knee-tissue regeneration and protective effects.

continued

Allogenic Mesenchymal Stem Cell Treatment for OA of the Knee.



- VAS Improvement over 2 yrs.
- Notice Group A with allograft stem cells of 50 x 10^6 had progressive improvement over the 2 year period.

Involving Patients

- Self Efficacy accounted for 14% of pain variation and 28% of overeating behaviors in obese patients with OA. (Pells JJ; Pain. 2008; 136(3):340-7)
- Self management arthritis programs had significant improvements (*P* 0.05) in self-efficacy, stretching and strengthening exercises, aerobic exercises, and general health. (Goeppinger J et al; Arthrits Rheum. 2007:57(6):1081-8)

Involving patients and families

- Involving spouses improved coping, self efficacy and physical disability. (Sharma et al;Curr Opinion Rheumatol.2002;14:603-7)
- Education of patients and families reduces pain and improves function similar to NSAIDs. (Creamer P.;Curr Opinion Rheumatol 2000; 12:450-55)

Closer Interaction

- Hand holding allows patients to walk faster and with less variability compared to guarding and walker alone (Balash Y; J Neural Tansm; 2007; 114(10): 1309-14)
- Social isolation caused increase incident as well as number of breast cancer tumors in mice. (Conzen S; Cancer Prevention and Research; 2009, Oct)
- Stronger Placebo Effects- Since 2001, the number of new drugs failing to show improvement over placebo in Phase III trials has risen over 11% . (Silverman S.; Wired Magazine; 2009, 9/17)

- **What does this mean ?**
- Holding hands- patients want someone to touch them and guide them.
- Social Isolation- patients want to be be part of a community or team.
- Stronger Placebo Effects- Patients want to believe you will do something to help them.

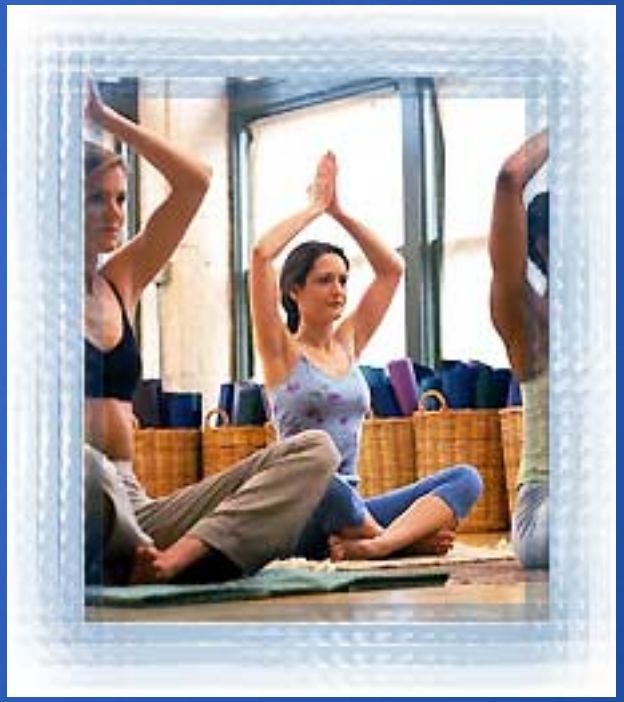
Community Involvement

- Community
- 68% of patients w/ arthritis are willing to attend groups for help.(Buckley: Arthritis Care Res, 1990)
- Sense of Coherence was a factor protecting against depression in patients with RA (Buchi: J. Rhuematol, 1998)

Few More Ideas

- Writing in a journal reduces painful joints

  (Smyth; JAMA, 1999)
- Meditation helps reduce joint pain (Singh;Alten Ther Health Med, 1998)
- Meeting with others improves outcome (Taal;Semin Arthritis Rheum,1997)



Summary

- Get the Pump Moving- Exercise
- Reduce Destruction- Weight Control, Shoe Wear
- Improve alignment of the pump- Wedges, Bracing
- Stimulate Repair- GS, HA, Micronutrients, PEMF, WBV, PRP, Stem Cell injections
- Educate patients and families to take charge and participate in their health care.

Non-operative Treatments of OA

- Thank You!
- Edward Loniewski, DO. FACOS , FAOAO

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