AN OVERVIEW:

Cartilage Treatment

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No Disclosure
The Science of Hyaline Cartilage
I. HYALINE CARTILAGE BASIC SCIENCE

Normal Anatomy

Cartilage is hypocellular, avascular, aneural tissue lining synovial joints

**Purpose:** facilitating lubrication and load distribution for joint movement

**Chondrocytes rest within lacunae and function to synthesize and maintain the matrix**

Cartilage is composed of:
- **Chondrocytes** that produce a large amount of collagenous extracellular matrix (ECM) to create cartilage
- **Extracellular matrix (ECM)**
  - Water (~65-80%)
  - Collagen
  - Proteoglycans

Cartilage exists in 2 distinct phases:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Composition</th>
<th>Function</th>
</tr>
</thead>
</table>
| Solid | Collagen: Primarily type II fibrils  
  Proteoglycans: Aggrecan is highly negative due to chondroitin and keratin sulfate groups > high water affinity | High resistance to fluid flow, compressive strength |
| Liquid | Water and ions: Located in interstitial interfibrillar space | Allows for reversible deformability and load dissipation |
## Zones of Articular Cartilage

<table>
<thead>
<tr>
<th>Zone</th>
<th>Components</th>
<th>Function &amp; Characteristics</th>
</tr>
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</table>
| **I. Superficial** | • Condensed type II collagen fibers (lamina splendens)  
• Fibers oriented parallel to surface  
• Flattened chondrocytes | • Shear stress resistance  
• Secretion of lubricative proteins  
• Low fluid permeability, high deformability |
| (Tangential)       |                                                                            |                                                                  |
| **II. Middle**     | • Random, oblique orientation of type II collagen fibers > increased compressive modulus  
• Round chondrocytes | • Transition point between resistance of shearing forces above and compressive forces below |
| (Transitional)     |                                                                            |                                                                  |
| **III. Deep**      | • Thick, type II collagen fibers with perpendicular orientation to surface  
• Low water concentration, high proteoglycan concentration | • Highest compressive modulus  
• Load distribution  
• Compressive resistance |
| (Radial)           |                                                                            |                                                                  |
| **IV. Calcified**  | • Tidemark separates this layer from deep radial layer  
• Cells embedded in matrix with apatitic salts | • Anchors above layers to the subchondral bone |
| Cartilage          |                                                                            |                                                                  |
Interaction between the solid and fluid phase of cartilage provides its viscoelastic properties

Fluid Phase – 80% of the weight is fluids

Hyaline Cartilage: Unloaded

Solid Phase – ECM – Porous & permeable

Hyaline Cartilage: Loaded

In response to weight bearing:

1. Contact forces between the articular surfaces increase interstitial pressure
2. Low permeability of the solid phase transfers pressure to the fluid phase
3. Strongly bound to hydrophilic proteoglycans, water in the interstitial space is displaced from the ECM
4. High friction resistance of the solid component creates drag, which pulls water back into the ECM and reverses deformation when forces are removed
I. HYALINE CARTILAGE BASIC SCIENCE

Response to Injury

The body always tries to repair itself. Cartilage injury does not follow the normal repair cycle – inflammation, repair and remodel.

Early Stage Chondrocyte Injury

- Injury to chondrocytes leads to decreased cell metabolic capability and impaired proteoglycan production.
- Low proteoglycan levels lead to increased tissue hydration and disarray of collagen fibrils.
- Decreased hydrostatic pressure results in transmission of loads to damaged cartilage.

Full-thickness Cartilage Injury

- Higher intrinsic repair as penetration of subchondral bone leads to hematoma formation, stem cell migration, and vascularization.
- Stem cells produce fibrocartilage, made of type I collagen, which exhibits inferior biomechanics to type II collagen.
- Continued cycle of degeneration and progression to osteoarthritis.

Cartilage Dilemma

Cartilage exhibits poor innate regenerative capabilities due to its low metabolic activity, avascularity and poor endogenous source of new cells.
Treatment Goals and Epidemiology
II. TREATMENT GOALS AND EPIDEMIOLOGY

Major Treatment Goals

1. Reduce Symptoms
2. Improve Function
3. Prevent Degradation

Epidemiology of Injury:

- 60-63% of patients undergoing arthroscopy found to have chondral lesions

- 58% of identified arthroscopic lesions are atraumatic

- 11% of traumatic, localized full-thickness lesions are ICRS class III and IV

Most common locations:
- Medial Femoral Condyle
- Lateral Tibia
- Patella

Most common associated injuries:
- Medial Meniscus Tears (37%)
- ACL Tears (36%)

References:
II. TREATMENT GOALS AND EPIDEMIOLOGY

Types of Treatment

**Palliative Treatment**
- **Chondroplasty:** Debridement of chondral lesion on the medial femoral condyle
  - Li et al. 2008

**Restorative Treatment**
- **Osteochondral Autograft transplantation (OATS):** Condylar surface after OATS procedure
  - Camp et al. 2014

**Reparative Treatment**
- **Microfracture (MFX) +/− StemCells Microdrilling:** Awl perforating subchondral bone
  - Perera et al. 2012
- **Osteochondral Allograft (OAG):** Allograft after insertion into femoral condyle defect
  - Yanke et al. 2015
- **Autologous Chondrocyte Implantation (ACI):** 2nd generation collagen membrane inserted via mini-arthrotomy
  - Mithoefer et al. 2012
Conventional Treatments
III. CONVENTIONAL TREATMENTS

Microfracture

Indications
• Unipolar (single compartment) lesions
• Better outcomes associated with:
  - Lesions < 2cm²
  - Active patients < 40 years
  - ICRS grade < 3 or 4
  - BMI < 30

Overview
Tiny fractures in the subchondral bone plate cause blood and bone marrow to seep out of the fractures

Rationale
Multipotent mesenchymal stem cells from the bone marrow may heal with repair tissue consisting of fibrous tissue

Debrided defect site with well-defined, perpendicular margin of healthy cartilage

Subchondral bone perforations spaced 2-3 mm apart to permit flow into chondral defect

Efflux of marrow elements into defect form fibrin clot, stimulating stem cell differentiation into fibrocartilage

Tetteh et al. 2012
III. CONVENTIONAL TREATMENTS

OATS (Osteochondral Autograft Transplantation)

**Indications**
- Unipolar chondral lesions of the distal femoral condyle
- Lesions < 2cm², size limited by donor site morbidity
- Patients < 50 years

**Overview**
Autologous cartilage plug with underlying subchondral bone grafted from low weight-bearing area

**Rationale**
Viable chondrocytes contained in the plugs along with the integration of subchondral bone facilitates the restoration of the overlying defect

- Debridement of recipient site
- Preparation of bone tunnel
- Insertion of osteochondral plug
III. CONVENTIONAL TREATMENTS

OAG
(Osteochondral Allograft Transplantation)

Indications
- Useful in cases with significant bone loss
  - OCD and AVN
- Revision technique for other joint preservation procedures
- Treatment of larger lesions

Overview
Cadaveric allograft (refrigerated max 14 days) with viable chondrocytes, mature harvested. Implanted into defect for integration with surrounding healthy tissue.

Rationale
Better outcomes associated with young patients, unipolar lesions
III. CONVENTIONAL TREATMENTS

C-ACI (Autologous Chondrocyte Implantation)

**Indications**
- Patients with significant functional demand, such as athletes
- Full thickness defects ranging 2-10cm²
- Young patients (<50 years of age)
- Therapeutic option following failure of other joint preservation procedures

**Overview**
Knee cartilage is biopsied from a less weight bearing area. The harvested chondrocytes are grown in vitro for approximately four to six weeks. In a second treatment the chondrocytes are applied to the damaged area via mini-arthotomy.

**Rationale**
Autologous cells adapt to their new environment and form tissue which exhibits qualities similar to native tissue.

- Arthroscopic chondrocyte harvest from lesser weight bearing area
- Defect is prepared with vertical boarders and down to the subchondral bone
- Type I/III collagen membrane seeded with chondrocytes
**MACI Technique**

**MACI** (autologous cultured chondrocytes on porcine collagen membrane)
Following arthroscopic assessment, cell harvest from low weight-bearing site, and cell expansion, implantation involves:

1. **Step 1:** Defect is accessed and debrided of damaged cartilage

2. **Step 2:** MACI Implant is cut according to template, matching defect size and shape

3. **Step 3:** Fibrin sealant is applied to the defect and bone bed for fixation of the membrane

4. **Step 4:** Implant is placed in the defect with proper membrane orientation: cells to bone bed, smooth side facing joint

5. **Step 5:** MACI Implant is held into place with light pressure and fixed by the fibrin glue

No suturing required, though suturing is possible if size or degree of containment demand.
Treatment Algorithm

Chondral Defect

Femoral condyle
Correct ligament instability, meniscal deficiency, malalignment

Defect size

≤ 2-3 cm²
- Younger/Higher demand
  - OAT ++
  - MFX ++

> 2.5-3 cm²
- Older/Lower demand
  - Palliative
    - OAT +
    - MFX ++
  - OCA ++
  - ACI ++

Patellofemoral
Address patellar malalignment as needed

Defect size

≤ 2-3 cm²
- Younger/Higher demand
  - ACI
  - OAT* +
  - MFX+
  - OCA* +/−

> 2.5-3 cm²
- Older/Lower demand
  - MFX ++
  - ACI* +
  - OCA* +
  - ACI* +
  - OCA* +
  - MFX ++
Emerging Therapies

Trilogy of Biology

- The Cells
- The Matrix
- The growth Factors
IV. EMERGING THERAPIES

Microfracture Augmentation

Limits to Microfracture (MFX)

- Fibrocartilage repair exhibits inferior strength and force distribution vs hyaline cartilage
- Inconsistent defect filling
- Rates of clot shrinkage or displacement up to 50%
- Poor fill rate predicts poor clinical outcomes
- Functional decline over 24-36 months
- Therapeutic results have limited lifespan of 2-3 years

MFX + Platelet-Rich Plasma (PRP)

PRP has been shown to augment both proliferation and differentiation of mesenchymal stem cells. (Krüger et al. 2012)

Medial femoral condyles at 12 months

[Images of MFX alone and MFX + PRP]
### IV. EMERGING THERAPIES

#### Additional Options

<table>
<thead>
<tr>
<th><strong>BST-CarGel®</strong></th>
<th><strong>Biocartilage®</strong></th>
<th><strong>Cartiform®</strong></th>
<th><strong>AMIC:Chondroglide®</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan polymer scaffold stabilizes efflux of bone marrow contents to allow formation of superclot.</td>
<td>Dehydrated, micronized cartilage allograft composed of type II collagen, proteoglycans and growth factors. High surface area matrix scaffold facilitates Mesenchymal Stem Cells (MSC).</td>
<td>Viable chondrocytes, growth factors and ECM proteins promote MSC differentiation towards native hyaline cartilage. Cryopreserved osteochondral allograft allows for 2-year shelf life.</td>
<td>3D Collagen I/III scaffold facilitates clot stabilization, MSC seeding and protection from the articular surface.</td>
</tr>
</tbody>
</table>

**BST-CarGel /whole blood mixture added dropwise to facilitate chondral defect filling.**

**Biocartilage product inserted into prepared patellar lesion.**

**Trochlear defect treated with Cartiform allograft.**

**Femoral condyle treated with Chondrogide® matrix.**

*Hoffman et al. 2015*
### Additional Options

<table>
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<th>Therapy Name</th>
<th>Description</th>
</tr>
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<tr>
<td><strong>Prochondrix®</strong></td>
<td>3D laser-edge cellular autograft with living chondrocytes. Available in dimensions from 7-20 mm and is stored fresh for 28 days max.</td>
</tr>
<tr>
<td><strong>Denovo NT® Juvenile Preserved Cartilage</strong></td>
<td>3D volume-stable construct of viable cartilage prepared from donor &lt; 13 years of age. Cartilage is manually minced into 1 cm³ cube.</td>
</tr>
<tr>
<td><strong>CartiONE™</strong></td>
<td>Combination of fresh chondrocytes and bone-marrow cells. A technician in the OR isolates and then mixes the cells, which are placed on a commercially available membrane.</td>
</tr>
</tbody>
</table>

- **Living chondrocytes in matrix**
- **Graft placed over a base of fibrin glue in the patella**
- **Carrier and CartiONE cells implanted in a defect**

Tompkins et al. 2013
## IV. EMERGING THERAPIES

### Off-the-shelf Osteochondral Techniques

<table>
<thead>
<tr>
<th><strong>MaioRegen™</strong></th>
<th><strong>Chondrofix®</strong></th>
<th><strong>BMAC</strong></th>
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<tr>
<td>Multi-layer Type I collagen-hydroxyapatite nanostructural biomimetic osteochondral scaffold aimed to induce MSC differentiation. Trials are ongoing in Europe.</td>
<td>Decellularized hyaline cartilage and cancellous bone allograft with 2-year shelf-life, eliminating donor tissue availability and safety issues. Prospective trials have reported a 72% success rate.</td>
<td>Bone-marrow derived mesenchymal stem cells are aspirated from the patient’s iliac crest. Activated in a centrifuge with an enzyme, they produce a “sticky clot” which is then implanted into the chondral defect.</td>
</tr>
</tbody>
</table>

MaioRegen implant in a chondral defect

Chondrofix graft embedded in a chondral defect

BMAC inserted into defect

*Courtesy of Alberto Gobbi Gomoll et al. 2013*
Rehabilitation
VI. REHABILITATION

Goals of Management

1. **Protect the repair site** by avoiding harmful forces and controlling load application

2. **Create a healing environment** with appropriate loads and knee mobilization

3. **Reduce pain and effusion** to maintain rehabilitation and mobility targets

4. **Maintain Mobility in relevant tissues** to restore soft tissue balance

5. **Enhance proprioception and neuromuscular control** focusing particularly important in later stages

6. **Restore muscular function** by focusing on the CORE muscle groups to reduce rotational and shear forces

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**Trunk Muscles (Core)**
- Abdominals
- Obliques
- Paraspinal

**LE Muscles**
- Quads
- Hamstrings
- Lat Gastroc

**Hip/Pelvis Muscles (Core)**
- Gluteus Medius
- Gluteus Maximus

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Individualized programs to match key factors:

**Lesion**
Location, size, depth, containment and quality of surrounding tissue

**Patient**
Age, (Biologic) BMI, general health, activity level, goals and motivation

**Surgery**
Repair procedure, tissue involvement and any concomitant procedures

**Surgeon**
Individual preference and familiarity


VI. REHABILITATION

Rehabilitation Overview

<table>
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<tr>
<th>Continuous Passive Motion</th>
<th>Begin 24 hours after surgery, continue through 4-6 weeks</th>
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<tr>
<td>Weight Bearing</td>
<td>Gradual progression to full weight at 8 weeks, as tolerated by the patient</td>
</tr>
<tr>
<td>Range of Motion</td>
<td>0-90° by week 3; increase by 10° per week to 135° Stationary bike at 4 weeks</td>
</tr>
<tr>
<td>Strengthening</td>
<td>Quadricep strength is restored initially followed by CORE lower extremities Elliptical trainer at 2-3 months</td>
</tr>
<tr>
<td>Impact Loading</td>
<td>Low impact 5-6 months; jogging 6-7 months Return to sports at 9-12 months, depending on sport and readiness</td>
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<td>Special Considerations</td>
<td>Low impact 5-6 months; jogging 6-7 months Return to sports at 9-12 months, depending on sport and readiness</td>
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CONCLUSION

Data suggests similar clinical outcomes between conventional treatments for smaller lesions at intermediate follow-up. With larger lesions, >2cm² you want to provide the best treatment option to restore functionality for an extended period of time.

**MFX is the most commonly performed:**
- Simple, cost-effective
- Early deterioration of clinical outcomes
- Increased risk of conversion to arthroplasty
- Augmentation

**MACI offers return to full functionality:**
- Two-step procedure requiring one open surgery; Cost
- For patients with significant functional demand, such as athletes
- Individualized rehabilitation program

**OAG performs similarly to MFX and ACI:**
- Requires donor tissue
- Requires refrigerated storage with limited lifespan
- Needs to be treated as a transplant

**OATS exhibits great outcomes for small lesions:**
- Similar cost-effectiveness to MFX
- Viable first line alternative to MFX
- Limited by donor site morbidity

Emerging therapies show initial promise but studies are needed to show efficacy.
Thank you