Repair of Articular Cartilage in Knee Joints

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Cartilage

Hyaline

Fibrocartilage

Elastic
Anatomy of Articular (Hyaline) Cartilage

Hyaline cartilage is the load bearing material of diarthrodial joints that possesses an extremely low coefficient of friction.

Lacks both blood supply and innervation.
Composition of Cartilage

The extracellular matrix is composed of a dense network of fine collagen (type II) fibrils enmeshed in a concentrated solution of proteoglycans.

Water makes up \( \sim 75\% \) of the wet weight of hyaline cartilage.
Three Structural Zones

- Superficial Tangential Zone (STZ)
- Middle Zone
- Deep Zone
Primary Forces Affecting Cartilage

Tensile

![Tensile modulus, $E = \sigma/\epsilon$](image)

- **Failure**
- **Linear region**
- **Toe region**

![Cartilage structures](image)

- Collagen
- Water
- Proteoglycan

**Uniaxial tensile loading**
Compressive
**Mechanical Properties**

**Viscoelasticity:** property of materials that exhibit both viscous and elastic characteristics when undergoing deformation allowing the material to present time dependent strain.

**Anisotropy:** the property of being directionally dependent.

**Tension Compression Nonlinearity:** the variables cannot be written as a linear combination of independent components. Tissue can be thought of as being bimodular.
Permeability: determines the flow of fluid through the material by an applied pressure gradient.

Inhomogeneity: Biomechanical properties are not uniform throughout the material.
Mechanical Properties (continued)

Mechano-Electrochemical Response: refers to the properties affected by the chemical constituents of cartilage

Lubrication: necessary for reduction of the friction coefficient and thusly aids in maintaining high wear resistance
Articular Cartilage Defects

Focal Defects
- trauma (impact, repetitive shear/torsional forces)

Complex Defects
- osteoarthritis
- primary (aging)
- secondary (genetics, obesity, injury)
- osteochondritis dissecans (OCD)
Articular Cartilage Defects

Grades of Damage:

- **Grade I**: Superficial lesions
- **Grade II**: Lesions are <50% cartilage depth
- **Grade III**: Lesions are >50% cartilage depth but do not extend into subchondral bone
- **Grade IV**: Lesions extend into subchondral bone
Debridement
(Abrasion Anthroplasty)

- Removal of unstable cartilage around affected region
- Some remodeling of joint surface
- Used in conjunction with other procedures
Bone Marrow Stimulating Techniques

Procedures:
- Drilling
- Micro-fracture

How they work:
- Piercing of the subchondral bone causing bleeding
- Release of pluripotent mesenchymal stem cells
- Growth of fibrocartilage
Drilling

Holes approx. 2mm in diameter are drilled into the subchondral bone exposed by the lesion.

Drilling has widely been replaced in clinical practice by micro-fracture due to thermal necrosis.

Development has gone into specialized drill bits and irrigation to combat bone necrosis.
Micro-Fracture

Small fractures are made in the subchondral bone with a sharp awl.

Micro-fracture has become the commonly accepted practice used to repair small lesions < 2.5 cm².
Bone Marrow Stimulating Techniques

Effectiveness:

- Relatively quick recovery time
- Relief of symptoms while cartilage is intact
- Forms fibrocartilage
- Functional decline of cartilage over time
Autologous Chondrocyte Implantation (ACI)

Biopsy of articular cartilage tissue (chondrocytes) is taken via arthroscopy.

Cells are grown in vitro for 3-6 weeks.

Methods of culturing cells involve a wide variety of different factors and are currently under development.

Original methods caused chondrocytes to lose their differentiated phenotype.
**Autologous Chondrocyte Implantation**

**First Generation ACI (ACI-P)**

- Debridement of defect area

- Peristoeal flap harvested from the proximal medial tibia is secured over defect area

- Cultured cells are injected underneath the flap

- Flap is sealed
Autologous Chondrocyte Implantation

Second Generation ACI (ACI-C)

- Bilayer collagen membrane (Chondro-Gide) is used in place of periosteal flap
- Prevents hypertrophy and donor site morbidity
Tissue Engineering provides the goal of developing an ideal method of treatment that will restore complete functionality of the joint.

It seeks to repair or regenerate damaged or diseased tissues using combinations of scaffolds, cells, and environmental cues such as bioactive molecules and physical factors.
Design Considerations

- Geometry control
- Time dependent with elastic component
- Resists impact loading
- Resists permanent deformation and fracture under cyclic loading
- Resists wear under cyclic articulation
- Adheres to adjacent tissue
Successful Implantation

Currently a lack of methods to test the in vivo mechanical properties of engineered cartilage.

Success currently determined by comparison to the competing methods.
Scaffolds

Function:

- promote cell proliferation and chondrogenesis
- models ECM
- provides structural support
- used in conjunction with Growth Factors
Scaffolds

Natural
- Fibrin, Alginate, Hyaluronan, Chitosan
- biocompatible

Synthetic
- Polyglycolic acid (PGA), Polylactic acid (PLA)
- Ease of production and better resistance over time
Signaling Molecules

Hormones, cytokines, and growth factors that influence both the development of chondrocytes and mesenchymal stem cells

Ability to promote cartilage repair has been indicated through studies conducted on different species and in vitro

Used in conjunction with scaffolds to achieve desired
Signaling Molecules

- Transforming Growth Factors alpha and beta (TGF-a, TGF-b)
- Bone morphogenic proteins
- Insulin-like Growth Factor-1 (IGF-1)
- Fibroblast Growth Factor
- Insulin-like Growth Factor-1 (IGF-1)
- Hyaluronic Acid (HA)
- Transcription factors (SOX-D)
TGF-Beta

**In vitro:** induces mesenchymal stem cells to chondrocytes, promotes cell proliferation, promotes protein synthesis, and suppresses matrix metalloproteinasis

**In vivo:** applied to defects in rabbits within a scaffold causing notable improvement in histology

**In excess:** can cause osteophytosis
Bone Morphogenic Protein

- Increase chondrogenic phenotype (collagen II, proteoglycan)
- Resistant to fibroblastic invasion
- Promotes ECM synthesis
- Osteophytosis and prevention of chondrocyte migration
Challenges with Growth Factors

Viable techniques to promote in vivo success

Timing of release

- Appropriate timing release of each growth factor to optimize chondrogenesis
- Overcoming short half-life of proteins and maintaining high concentration
  - repeat local administration
  - gene therapy (complimentary DNA)
Use of Mesenchymal Stem Cells

Use of Bone-Derived MSCs And Chondrogenesis In Vitro; Treatment for Osteoarthritis

Undifferentiated Mesenchymal Stem Cells (MSCs) From Adult Human Bone

MSC Pellet Culture

Cartilage

Hyaline Cartilage

Collagen Fibrils

Remove Bone Marrow

Replace Articular Cartilage Surface
Bone Marrow Derived Mesenchymal Stem Cells Compared to ACI

- better proliferation rate than chondrocytes
- Bone marrow biopsy is less invasive than knee arthroscopy (less donor site morbidity)
- 1 less general or regional anesthesia application is required; consequently the cost is less.
- Able to harvest a sufficient number of cells
ACI and BMSC Implantation hold great promise for future development of tissue engineered cartilage.

The refinement of tissue-engineering techniques will include evaluation of different cell-scaffold combinations, genetic manipulation of implanted cells and use of alternative biomaterials.

Future research should be aimed at investigating and evaluating tissue-engineering approaches to cartilage repair in disease-compromised models to gain a better understanding of clinically feasible designs.
References


