Biologic Augmentation for Meniscus Repair

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Scott Rodeo, M.D.
Co-Chief Emeritus, Sports Medicine and Shoulder Service
Co-Director, Orthopaedic Soft Tissue Research Program
Professor, Orthopaedic Surgery, Weill Medical College
Attending Orthopaedic Surgeon, The Hospital for Special Surgery
Team Physician, New York Giants Football
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What is the biologic target?

- Increased vascularity?
- Stimulation of cell proliferation?
- Cell chemotaxis?
- Synovial cell homing to meniscus?
- Accelerated matrix synthesis?
- Improved matrix remodeling?
My desired “biologic targets”

• Stimulate synovial cell “homing” to repair site
• Stimulate cell proliferation and new matrix synthesis
• Ameliorate excessive inflammatory response and associated protease activity
What is available to the clinician today?

What is the evidence??
Synovial Abrasion to Stimulate a Healing Response
Evidence for Synovial Abrasion

- Arnoczky: Dog model: Meniscus lesion connected to peripheral synovial tissue heals by fibrovascular scar (American J. Sports Med, 1983)

- Hypertrophic synovium expresses cytokines in rabbit model (Ochi, Arthroscopy 2001)

- Not effective for tear that is farther from synovial rim in sheep model (Nakhostine, Arthroscopy 1990)

- Positive results in limited clinical studies but no control group
30cc whole blood. Gentle stirring in glass vessel. Approx 1-2cc clot.
Fibrin clot
Fibrin clot
Evidence for Fibrin Clot

Arthroscopic meniscal repair using an exogenous fibrin clot


- Exogenous fibrin clot injected in the seam of the tear
- Isolated tear failure rate: 41% without exogenous fibrin clot versus 8% with clot
- Isolated repairs heal significantly better with exogenous fibrin clot injection

Use of the fascia sheath coverage and exogenous fibrin clot in the treatment of complex meniscal tears


- Exogenous blood clot is injected in the tear under fascial sheath
- Improved healing rates for complex meniscus tears

Arthroscopic Meniscal Repair With Fibrin Clot of Complete Radial Tears of the Lateral Meniscus in the Avascular Zone

van Trommel et al, Arthroscopy 1998

- Tear extending to popliteus tendon  N=5
- All healed at 2nd look arthroscopy
Microfracture of intercondylar notch
Evidence for microfracture of intercondylar notch

Marrow Stimulating Technique to Augment Meniscus Repair
Freedman et al. Arthroscopy 2003

- Microfracture of the intercondylar notch to provide marrow elements to the healing meniscus

Outcomes After Biologically Augmented Isolated Meniscal Repair With Marrow Venting Are Comparable With Those After Meniscal Repair With Concomitant ACL Reconstruction

- “Marrow venting” technique equivalent to hemarthrosis in ACL reconstruction
- Effective biologic augmentation technique
Platelet-Rich Fibrin Matrix in Meniscus Repair
Platelet-rich plasma/platelet-rich fibrin matrix

18 yr. old male isolated tear of popliteo-meniscal fasciculus → meniscus instability
18 yr. old male isolated tear of popliteomeniscal fasciculus → meniscus instability
Evidence for PRP / PRFM

**PRP in meniscal repair: does augmentation improve surgical outcomes?**  
*Griffin et al, Clinical Orthopaedics and Related Research 2015*

- Cascade platelet-rich fibrin matrix  15 with PRP, 20 no PRP
- No difference between groups

**PRP for open meniscal repair in young patients: any benefit?**  
*Pujo et al, Knee Surg Sports Traumatol Arthroscopy 2015*

- Open repair of horizontal meniscus tear  17 with PRP, 17 no PRP
- 24 mos. F/U: PRP group better for KOOS pain and sports parameters (p < 0.05)
- MRI: N=5 with complete disappearance of signal abnormality in PRP group

**Prospective, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Meniscal Healing, Outcomes, and Safety in Patients Undergoing Meniscal Repair of Unstable, Complete Vertical Meniscal Tears Augmented with PRP**  
*Kaminski R et al, Biomed Res Int. 2018*

- Prospective, randomized, double-blind, placebo-controlled  N=37
- Leukocyte-rich PRP vs saline
- Higher meniscus healing rate in PRP-treated based on MRI and/or 2nd look arthroscopy  (85% versus 47%,  P = 0.048)
Cell therapy

Meniscus root repair augmented with bone marrow aspirate concentrate
Repair of horizontal cleavage tear after saucerization of discoid lateral meniscus
Evidence for Cell Therapy

**Bone Marrow Aspirate Concentrate for the Treatment of Avascular Meniscus Tears in a One-Step Procedure-Evaluation of an In Vivo Model**

*Koch et al, Int J Mol Sci. 2019*

- New Zealand White rabbits  Meniscus repair +/- BMAC
- BMAC significantly improved healing

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**Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study**

*Vangsness et al. J. Bone and Joint Surgery 2014*

- Allogeneic bone marrow-derived cells injected 7-10 days after medial meniscectomy
- N=55
- MRI evidence of moderate meniscus regeneration: Increased meniscal volume by MRI in 24% of patients in lower cell dose group
- VAS and Lysholm score improvements
Cell-Based Approaches for Meniscus Healing

Very little data!

• Pak et al, BMC Musculo Disorders 2013:
  – N=32   Adipose-derived stem cells + PRP + hyaluronic acid
  – VAS/function improved, MRI evidence of meniscus regeneration

• Pak et al, Biomed Research Int. 2014:
  – N=1   Adipose-derived stem cells + PRP + hyaluronic acid
  – VAS/function improved, MRI evidence of meniscus regeneration

• Whitehouse et al, Stem Cell Translational Medicine 2017:
  – N=5   Autologous marrow-derived cells on collagen scaffold
  – 3/5 showed good results and MRI evidence of meniscus healing

Conclusions..??!!
Evidence for Cell Therapy: Synovial Cells are Promising

Synovial mesenchymal stem cells promote the meniscus repair in a novel pig meniscus injury model
Ozeki, Sekiya, et al, J. Orthopaedic Research 2021

- Meniscus injury model in microminipigs
- Treated with allogeneic synovial cell MSC suspension
- Histology, MRIs, and polarized microscopy showed that transplantation of synovial MSCs improved meniscus healing.

Additional Use of Synovial Mesenchymal Stem Cell Transplantation Following Surgical Repair of a Complex Degenerative Tear of the Medial Meniscus of the Knee: A Case Report
Sekiya et al. Cell Transplant. 2019

- N=5 patients with degenerative medial meniscus lesions treated with synovial MSCs
- Synovial tissue biopsy → cultured expanded for 14 days → synovial MSC cell suspension delivered to repair site
- Patients reported significant clinical score improvement by 2 years and 3D MRI scan showed no evidence of tear at the repair site
Complex Meniscus Tears Treated with Collagen Matrix Wrapping and Bone Marrow Blood Injection: A 2-Year Clinical Follow-Up

Tomasz Piontek¹, Kinga Clemmewska-Gorzela¹, Jakub Naczki¹, Roland Jakob³, Andrzej Szuś³, Monika Grygorowicz³, and Michal Słomczykowski²

Abstract
Objective To collect and analyze the 2-year follow-up clinical and MRI results of patients treated with an arthroscopic technique of collagen membrane-based meniscus repair. Design 53 consecutive patients with combined (horizontal and radial or longitudinal component) and complex meniscal tears (torn extended through avascular zones and/or composed with two or more morphological tear patterns) were treated with an "all-inside" arthroscopic suturing of meniscus and wrapping with a collagen membrane (Chondro-Gide) technique with bone marrow blood injection. The IKDC 2000 subjective score, IKDC 2000 clinical evaluation score, Lysholm score and Barrot clinical criteria of meniscal healing were recorded. All patients were examined by MRI 2 years postoperatively, using modified WOMS criteria for meniscal integrity. Results The 2-year follow-up was achieved in 50 cases. Of these, 2 patients were excluded from the evaluation due to incomplete data and 2 patients underwent partial meniscectomy and were classified as failures. In 46 patients (86.5% of the intended to treat cases), a statistically significant improvement in IKDC 2000 subjective, Lysholm scores and IKDC 2000 clinical assessment between preoperative and the 2-year follow-up time points were observed. Barrot criteria demonstrated an improved clinical outcome between pre- and post-operative values. MRI revealed a non-homogeneous signal without meniscal tear (WOMS grade 1) in 76% of the operated meniscus (WOMS grade 2). Conclusions The 2-year follow-up data demonstrate that this technique is safe and can offer an additional tool to save the meniscus in the patients otherwise scheduled for meniscal removal. Level of evidence IV

Keywords meniscus wrapping, collagen membrane, arthroscopic, complex, combined

Introduction
Meniscal injuries located in the low or nonvascularized zones (red-white and white-white zones) are often treated with partial or total meniscectomy. Although meniscectomy is a relatively simple and quick surgery with good immediate postoperative clinical outcomes, the long-term results are poor.¹⁻¹² These poor outcomes are not surprising since many studies have demonstrated the importance of the meniscus for the knee function.¹³⁻¹⁴ It has also been accepted that surgeons should preserve as much meniscal tissue as possible. Both complete and partial meniscectomy are associated with early degenerative osteoarthritis.¹⁵⁻¹⁷ To preserve function of the knee joint, it is now suggested that meniscal tears should be treated by meniscal repair instead of meniscectomy whenever possible.¹⁸⁻²₀ Various augmentation techniques for meniscal repair have been described. They include use of a fibrin clot, platelet-rich plasma, pro-inflammatory cytokines, and application of growth factors.¹⁹⁻²₀ Further progress in meniscus healing has been made possible by the innovative use of cells and scaffolds.²⁰ Improved methods to isolate and concentrate mesenchymal stem cells from autologous sources (e.g., bone marrow or adipose tissue) allows the evaluation of the role of cells-based techniques to augment healing. Furthermore, the development of advanced scaffold materials and associated techniques has contributed to creating an intracapsULAR biological environment for improved meniscal healing. Notably, Jakub and...
Complex meniscus tears treated with collagen matrix wrapping
Complex meniscus tears treated with collagen matrix wrapping
Evidence for Collagen Scaffolds

Complex Meniscus Tears Treated with Collagen Matrix Wrapping and Bone Marrow Blood Injection: A 2-Year Clinical Follow-Up
Piontek et al, Cartilage 2016

- Chondroguide collagen membrane "wrapped" around the meniscus tear site, followed by bone marrow injection  N=53
- No control/comparison group
- Significant improvement in IKDC and Lysholm scores at 2-year follow-up
- Follow-up MRI demonstrated no meniscal tear in 76% of the operated menisci

Use of the fascia sheath coverage and exogenous fibrin clot in the treatment of complex meniscal tears

- Exogenous blood clot is injected in the tear under fascial sheath
- Improved healing rates for complex meniscus tears
What can we practically use?

My current approach

- Synovial abrasion
- Microfracture intercondylar notch
- Consider leukocyte-poor PRP
- Combine with thrombin and calcium chloride to form a clot
What can we practically use?

My current approach

• Need to consider the role of mechanical load on biology of meniscus healing - implications for postoperative rehabilitation

• Consider tear pattern:
  – Partial compressive loading in extension for vertical longitudinal tear
  – Minimal load for radial or complex tear pattern
Future options to consider

- Simvastatin: Stimulation of fibrocartilage formation
- Tranexamic acid: Fibrinolysis inhibitor
- Losartan: TGF-β inhibition
- Low intensity pulsed ultrasound (LIPUS)
- Tissue adhesives
- Modulation of the intra-articular milieu:
  - IL-1β inhibition (Anakinra?)
  - TNF-α (Enbrel?)
  - MMP inhibition
- Immune cell subpopulations:
  - T regulatory cells, dendritic cells, NK cells etc.
- Stimulation of intrinsic stem cell niche in meniscus and synovium
THANK YOU

Sports Medicine and Shoulder Service
The Hospital for Special Surgery